# Deletion 4q35/duplication 10p15 associated with allergy and arthritis.

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## Family history

A familial cryptic reciprocal translocation between 4q35 and 10p15 leading to partial duplication of chromosome 10 and partial deletion of chromosome 4 was studied (Fig. 1). The propand is a 11 years old girl presenting with long philtrum, hypotelorism, broad mouth and mild mental retardation (Fig. 2). She has rheumatological and immunological diseases and symtoms including frequent infections, pulmonary infections, hypogammaglobulinemia, low IgG count, juvenile chronic arthritis with polyarticular symptoms since age 5, frequent stomach pains and inflammatory bowel disease. She also had congenital hydronephrosis and ASD with right-to-left shunt. Her parents are phenotypically normal but the maternal sister is multiallergic.

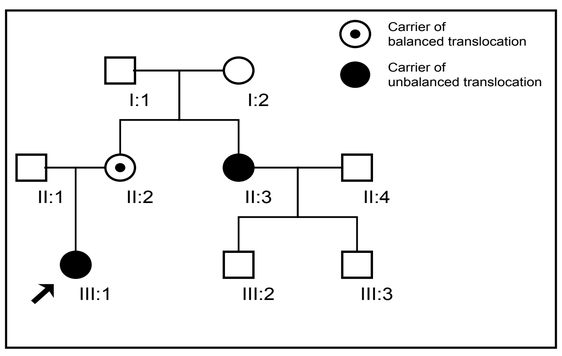


***Fig. 1**. Pedigree of the family with a cryptic translocation between 4q35 and 10p15.*

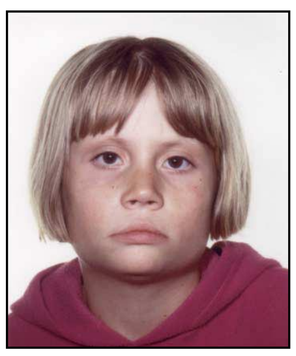

***Fig. 2***

## Materials and Methods

***CGH:*** Patient DNA and normal reference DNA were labeled with FITC-12-dUTP and Texas Red-5-dUTP(DuPont, Boston, MA, USA), respectively. Four hunderen ng of each DNA and 20$\mu$g cot1 DNA were hybridised to normal metaphase chromosomes. Slides were hybridised for 4 days, washed, and counterstained with 4,6-diamidino-2-phenylindole. CGH image capture was performed with a Cyto Vision (Applied Imaging, Sunderland,UK) interfaced to a DMRBE fluorescence microscope (Leica, Heerbrugg, Switzerland) and images were transferred to a Magiscan image analysis system (Applied Imaging, Sunderland, UK). In each case, 10 metaphases were analysed. Detection of aberrations was performed using standard reference intervals as described in Kirchhoff et al. (1998).

***FISH Mapping:*** BAC clones used in this study were selected from the RP-11 library and obtained from the MCN Reference Center at the Max Planck-institute for Molecular Genetics, Berlin (http://www.molgen.mpg.de/ ). FISH was carried out using 200 ng BAC DNA using standard protocols. DNA was labeled with biotin-14-dATP (Invitrogene) by nick-translation and hybridized to metaphase chromosomes prepared from the proband, the mother and the mothers sister. Signals were visualized using avidin-FITC detection system. Chromosomes were counterstained with 4,6-diamino-2-phenylindole (DAPI) and signals were investigated using a Leica DMRB epifluorescence microscope equipped with a Sensys 1400 CCD camera (Photometrics, USA) and an IPLab Spectrum imaging software (Vysis, USA).

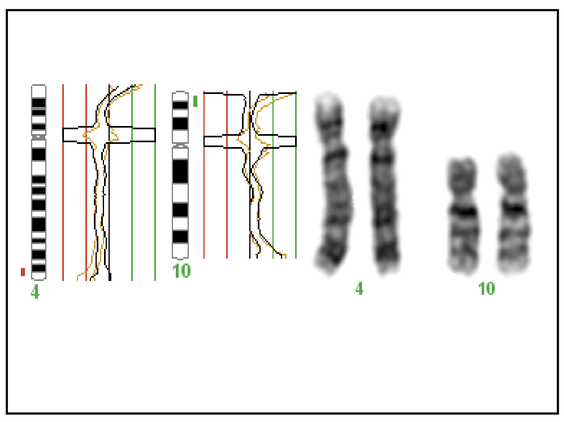


***Fig. 3***

## Results

***CGH studies:*** G-band analysis indicated a normal karyotype 46,XX, but high resolution CGH (HR-CGH) analysis revealed reduced material on 4qter (dim(4q35)) and additional material on distal 10p (enh(10p15)) in the proband (Fig. 3). The same imbalance was detected by HR-CGH in the maternal sister.

***FISH studies:*** A balanced reciprocal translocation t(4;10)(q35;p15) which could not be seen by classical banding analysis, was demonstrated in the mother by chromosome painting (not shown). FISH mapping with BAC probes indicated that 4q35.1-qter was deleted and 10pter-p14 was duplicated in the maternal sister (Fig. 4a,b), confirming the CGH results.

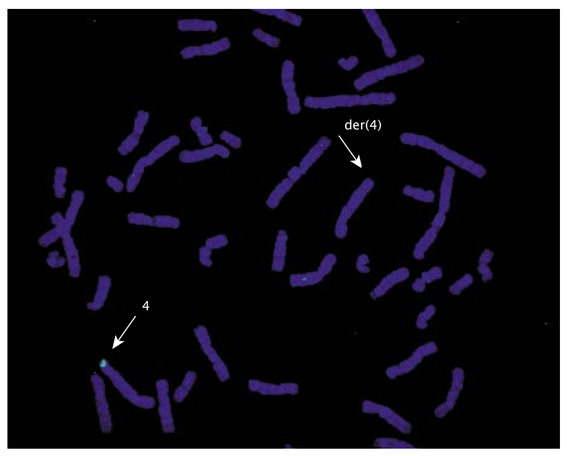


***Fig. 4a.** Deletion of 4q35 revealed by absent signal of BAC RP11-188D17 on der(4).*

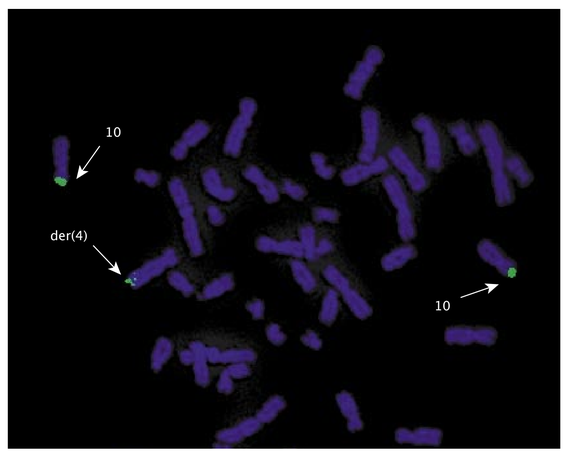


***Fig. 4b.** FISH with BAC RP11-145I2, showing signals on the two normal chromosomes 10 and the extra signal on der(4).*

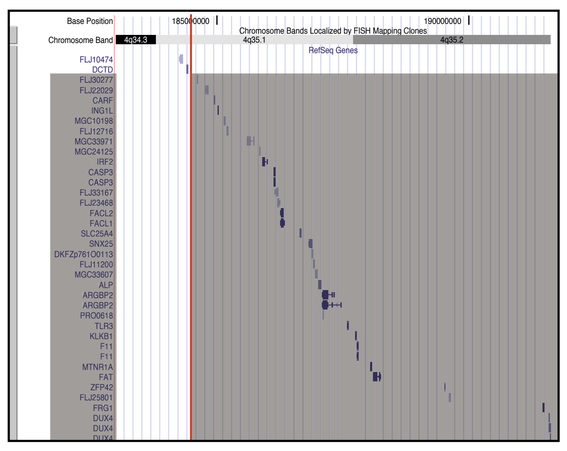


***Fig. 5a.** Gene content of the 4q35 region deleted in the proband and in her maternal sister (grey area). Red line indicate the translocation breakpoint (UCSC Genome Browser Nov. 2002 version).*

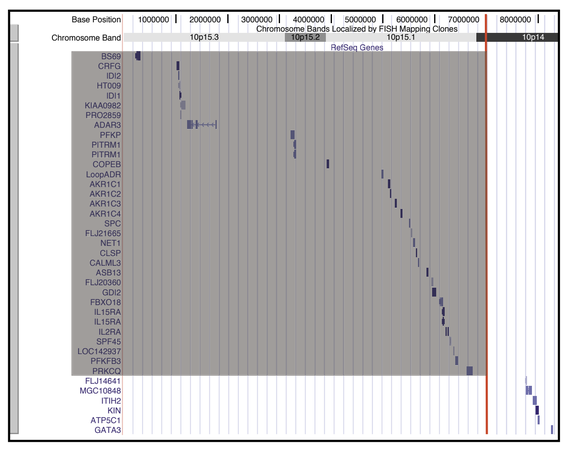


***Fig. 5b.** The 10p15 region duplicated in the proband and in her maternal sister (grey area). Red line indicate the translocation breakpoint (UCSC Genome Browser Nov. 2002 version).*

## Discussion

The cryptic translocation segregating in this family has in two instances resulted in the same unbalanced karyotype with a deletion of approx. 5 Mb of the terminal region of 4q35, and duplication of appr. 7 Mb on distal 10p15. In both cases this was accompanied by the the presence of immunological disturbances, most notably in the proband. Both the proband and her maternal sister had deleted the repeated units on terminal 4q35 that are deleted in facioscapulohumeral muscular dystrophy (FSHD), confirming that larger deletions involving additional material proximal to the FSHD repeats does not result in FSHD. Immunological disturbances have not been described so far in association with either distal deletion 4q35 or distal duplication 10p15. However, there are several genes which potentially could be associated with immunodysfunction: protein kinase C-theta (PRKCQ); interleukin 2 receptor, alpha chain precursor (IL2RA); and interleukin 15 receptor, alpha (IL15RA) on 10p15, and toll-like receptor 3 (TLR3) and interferon regulatory factor-1 (IRF1) on 4q35 (Fig. 5a,b).

**References**

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