CRYPTIC DUPLICATION AND DELETION OF 9q34.3→qter IN A FAMILY WITH A t(9;22)(q34.3;p11.2)

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ABSTRACT
A newborn male with a diagnosis of multiple congenital anomalies was referred to our laboratory for a high resolution chromosome study. These anomalies included congenital heart disease, micrognathia, a round face, hypertelorism, telecanthus, small ears, a short upturned nose with anteverted nares, and short toes. Chromosome analysis revealed what looked like satellite material on 9qter. FISH studies revealed the loss of subtelomeric region of 9q and the presence of acrocentric p-arm material on the der(9). DNA microarray analysis was performed which confirmed the breakpoint at 9q34.3. Familial chromosome and FISH studies were performed which revealed that the mother as well as the maternal grandfather were carriers of a balanced translocation involving chromosomes 9 and 22. This patient’s karyotype was therefore reported as 46,XY,der(9)t(9;22)(q34.3;p11.2) mat. The maternal great-aunt of the proband was found to have the opposite unbalanced rearrangement. Her karyotype was reported as 46,XX,ish der(22)t(9;22)(q34.3;p11.2). This maternal great-aunt and one of her daughters had a deletion of 9q34.3→qter where the 22p material involved is clinically irrelevant. The deletion of 9q34.3→qter resulted in a clinically affected severe phenotype, whereas the duplication of that region had negligible phenotypic effect. Many of the clinical features observed in our patient were also reported in the literature with a 9q34.3→qter deletion. Subtle deletions and duplications of the terminal light G-banding regions of different chromosomes have variable implications; therefore, a thorough and extensive analysis using FISH and/or DNA microarray studies are imperative to rule out or redefine the deletion/duplication more accurately and to correlate the clinical outcome with similar reported cases, if any.

METHODS
- Prometaphase chromosome analysis was performed utilizing standard cytogenetic procedures for high resolution studies.
- FISH analysis was performed on metaphase cells utilizing commercially available probes which included an acrocentric p-arm probe, a whole chromosome 9 paint probe and several probes specific for 9q34.1 – 9q34.3 including BCR/ABL, ASS and 9qtel.
- DNA Microarray analysis (Genosensor Array 300) was performed with DNA extracted from fibroblast cultures. Briefly, 100ng of DNA was differentially labeled with a reference female DNA and co-hybridized to the array according to manufacturer’s instructions (Abbott-Vysis, Downer’s Grove, IL).

RESULTS
- Prometaphase chromosome analysis of the proband revealed the presence of a “satellited” 9q terminal region. Parental chromosome studies revealed that the mother also had the satellited 9.
- FISH studies revealed a deletion of 9qtel (9q34.3) and the presence of acrocentric p-arm material in its place. The der (9) was also positive for ASS (9q34.1) and ABL (9q34.1). FISH studies on the mother revealed that the 9qtel was translocated to the short arm of chromosome 22.
- DNA microarray analysis confirmed the chromosome 9 breakpoint in band 9q34.3.

DISCUSSION
This family exhibits very interesting cytogenetic findings involving a pure duplication and a pure deletion of 9q34.3→qter where the 22p material involved is clinically irrelevant. The deletion of 9q34.3→qter resulted in a clinically affected severe phenotype, whereas the duplication of that region had negligible phenotypic effect. As seen with many chromosomal rearrangements, this family represents an example where a deletion of a chromosomal region is more detrimental than a duplication of that region.

Many of the clinical features observed in our patient were also reported in the literature with a 9q34.3→qter deletion. Some of these common clinical features include hypotonia, microcephaly, frontal bossing, epicanthal folds, hypertelorism, short nose, macro glossia and congenital heart disease.

This small deletion would have been difficult to detect had it not been for the satellites of chromosome 22 translocated to 9q34.3. Other patients in the literature with this deletion were detected as part of a subtelomeric scanning study. Most likely the majority of 9q34.3→qter deletions are not diagnosed with high resolution studies. Current FISH and DNA microarray technology enabled our lab to determine that the two subtelomeric probes were deleted with the retention of the ABL and ASS loci in 9q34.1. Therefore, it is suggested that whenever a patient is seen with these similar clinical findings, subtelomeric FISH and/or DNA microarray technology should be utilized to rule out or confirm a deletion of 9q34.3→qter.