CASE REPORT

Use of single nucleotide polymorphism microarrays to distinguish between balanced and normal chromosomes in embryos from a translocation carrier

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Objective: To prove the ability to distinguish between balanced and normal chromosomes in embryos from a translocation carrier.
Design: Case report.
Setting: Academic center for reproductive medicine.
Patient(s): Woman with a balanced translocation causing Alagille syndrome seeking preimplantation genetic diagnosis (PGD).
Intervention(s): Blastocyst biopsy for PGD.
Main Outcome Measure(s): Consistency of 3 methods of embryo genetic analysis (real-time polymerase chain reaction, single nucleotide polymorphism [SNP] microarray, and fluorescence in situ hybridization [FISH]) and normalcy in the newborn derived from PGD.
Result(s): PGD was applied to 48 embryos. Real-time polymerase chain reaction, SNP microarray, and FISH demonstrated 100% consistency, although FISH failed to detect aneuploidies observed by comprehensive SNP microarray-based analyses. Two blastocysts were identified to be normal for all 3 factors using SNP microarray technology alone. The 2 normal embryos were transferred back to the patient, resulting in the delivery of a healthy boy with a normal karyotype.
Conclusion(s): This is the first report of validation and successful clinical application of microarray-based PGD to distinguish between balanced and normal chromosomes in embryos from a translocation carrier. (Fertil Steril® 2011;96:e58–65. ©2011 by American Society for Reproductive Medicine.)

Key Words: Aneuploidy, preimplantation embryo, Alagille syndrome, translocation, microdeletion

It is estimated that 1 in 625 individuals carries a balanced translocation (1). In most cases, carriers are phenotypically normal, but they are at increased risk for clinical pregnancy loss and offspring with congenital abnormalities and/or mental retardation as a result of unbalanced segregation during gametogenesis. A clinical phenotype may also result if there is disruption of critical gene(s) at the breakpoint regions. Studies using newer molecular cytogenetic techniques have now demonstrated that microdeletions are responsible for a proportion of cases in which an apparently balanced translocation is associated with phenotypic abnormality (2–4). In fact, small genomic imbalances such as microdeletions, as well as duplications or inversions, occur at or near the chromosomal breakpoint in 10% to 60% of cases (4–12). A good example is Alagille syndrome (ALGS), which is caused by mutations in the Jagged1 gene (13, 14). There are now a few reports of patients with ALGS with apparently balanced translocations, all of which share a common breakpoint on chromosome 20 at p12.2 (13–15). A microdeletion encompassing the Jagged1 gene has been demonstrated in some of these cases (13, 14) and presumed in the others.

Individuals carrying this type of genetic abnormality who are interested in producing healthy offspring through preimplantation genetic diagnosis (PGD) would require more careful screening than is currently available. The primary aim of PGD would be to distinguish between embryos carrying the "balanced" translocation (and accompanying microdeletion) and those with truly normal chromosomes. A previously developed single nucleotide polymorphism (SNP) microarray–based method of aneuploidy screening (16)

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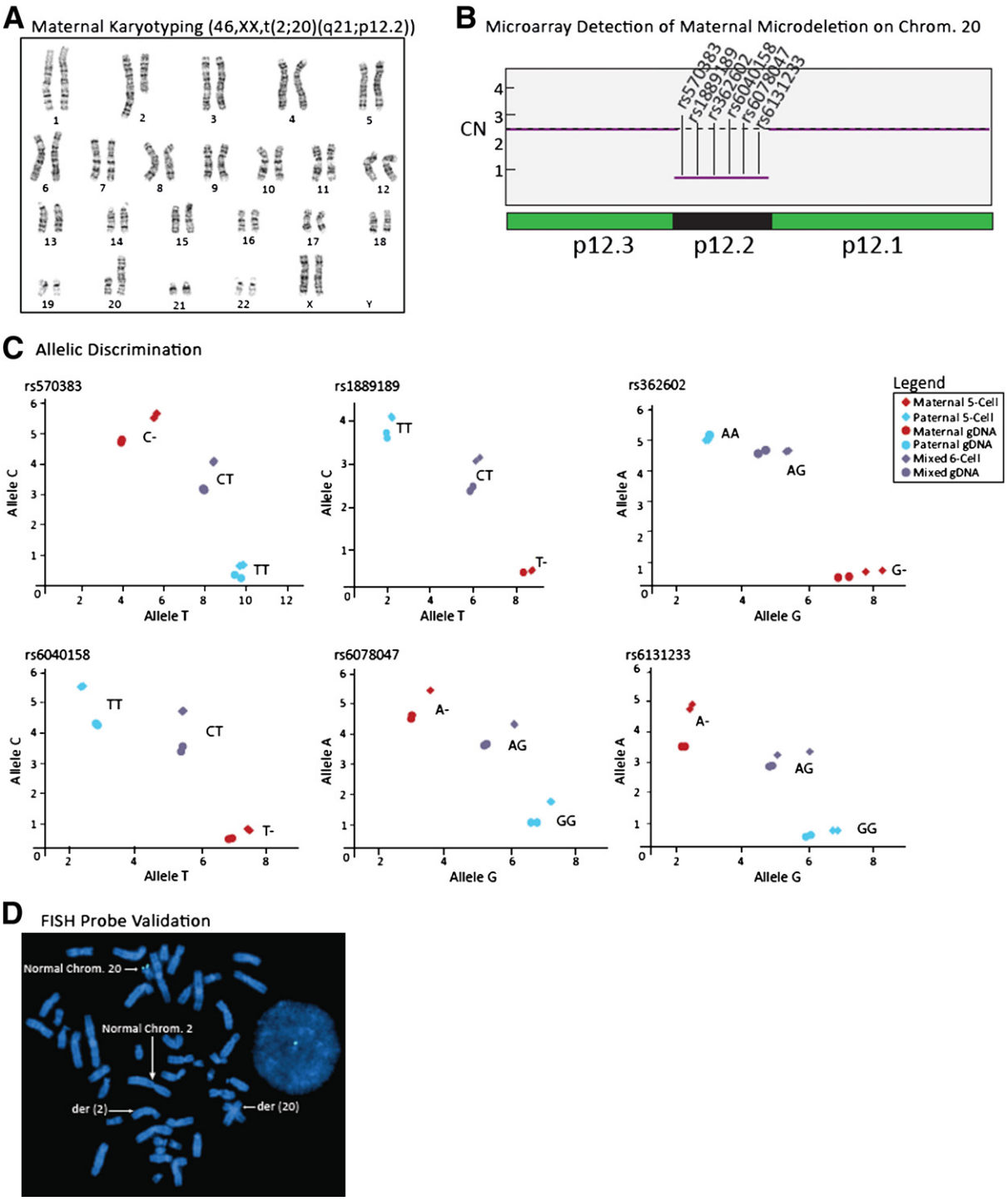
FIGURE 1

Workup results of a patient with ALGS. (**A**) Conventional karyotype analysis confirmed an apparently balanced translocation, 46,XX,t(2;20)(q21;p12.2). (**B**) SNP oligonucleotide microarray analysis copy number (CN) analysis of chromosome 20 revealed a microdeletion (including the Jagged1 locus) that causes ALGS. The expanded view of cytoband 20p12.2 indicates the dbSNP rs identifiers for each of the 6 SNPs identified as informative and used in the subsequent triple-factor PGD of embryos derived from the patient during 2 IVF cycles. (**C**) Real-time polymerase chain reaction results for lymphocyte samples from the patient, partner, or mixture of the 2 illustrating the expected genotypes of homozygous opposite for each intended parent and heterozygous for the mixtures. Genomic DNA of each sample served as a control for the expected genotypes of the 5-cell samples. (**D**) Confirmation of the 2.36-Mb deletion using fluorescence in situ hybridization (FISH) with probe RPC-11-1056I10 (Jagged1 locus). Only 1 copy of the Jagged1 locus, on the normal chromosome 20, is present.



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