Kraft and Stram[2] should be viewed with great caution. First, the maximum-likelihood method implemented in their simulation study pertains to the prospective likelihood, which ignores the case-control sampling. Second, the inclusion of haplotypes with very low frequencies can cause numerical instabilities. Third, the setup of 32 haplotypes with equal frequencies is highly unrealistic.

Imputation can be a good approximation of maximum likelihood in many situations but can never be superior. Given the availability of HAPSTAT and other user-friendly software, there is no strong reason to not use proper maximum likelihood.

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Impact of Array Comparative Genomic Hybridization–Derived Information on Genetic Counseling Demonstrated by Prenatal Diagnosis of the TAR (Thrombocytopenia-Absent-Radius) Syndrome–Associated Microdeletion 1q21.1

To the Editor: The latest array-based genome-scanning methods are beginning to revolutionize clinical genetics.[1] Prominent recent examples derived from array technologies include the identification of new microdeletion syndromes, such as the 17q21.3 microdeletion syndrome (MIM 610443),[2–4] and the elucidation of genomic loci harboring genes for CHARGE (MIM 214800)[5] and Pitt-Hopkins syndrome (MIM 610954).[6–8] Furthermore, array applications revealed a plethora of copy-number variations (CNVs) in the human genome.[9] Some of these CNVs likely contribute to complex human disorders such as Crohn disease (MIM 266600)[10] and autism.[11,12] An especially interesting contribution of array comparative genomic hybridization (array-CGH) has been helping to unravel the cause of thrombocytopenia-absent-radius syndrome (TAR) (MIM 274000), a rare syndrome characterized by bilateral absence of the radii with presence of both thumbs and thrombocytopenia,[13] which was published in the February 2007 issue of the *Journal*.[14] Klopocki et al.[14] reported that TAR syndrome has a complex pattern of inheritance associated with a common interstitial microdeletion of 200 kb on chromosome 1q21.1 and an additional, as-yet-unknown modifier. This microdeletion was not present in 700 control samples and has not yet been described in the Database of Genomic Variants.[14]

To exemplify how the new knowledge derived from array-based analyses extends our ability to improve genetic counseling, we describe here the prenatal case of a nonconsanguineous couple. The 42-year-old pregnant woman (G_2P_0 at the time of counseling) and her 45-year-old husband were referred to our genetic counseling service. During ultrasound examination at a gestational age of 16 wk, bilateral phocomelia was found. No other abnormalities were noted at that time, and the hands were not well visualized. During the woman's first pregnancy, phocomelia had also been noted at a gestational age of 14 wk, and the pregnancy was terminated at the 22nd gestational week. At this time, chromosome analysis from amnion cells revealed a normal female karyotype (46,XX), and no further analysis had been done. Both parents had an unremarkable phenotype.

If phocomelia is diagnosed during prenatal ultrasound examination, the most important differential diagnoses include TAR (MIM 274000), Holt-Oram (MIM 142900), and Roberts syndrome (MIM 268300). In the latter two conditions, the thumb is usually absent or severely hypoplastic. However, hands may not always be well visualized during an ultrasound, and occasionally patients with Roberts syndrome may exhibit normal thumbs.[15] Thus, on the basis of ultrasound examination alone, a definite diagnosis is impossible. In both TAR and Holt-Oram syndromes, conventional cytogenetic analysis usually yields normal karyotypes, whereas ~80% of cases with Roberts syndrome exhibit a chromosomal phenomenon known as "premature centromere separation."[16] Therefore, conventional chromosome banding analysis is often inconclusive. As a consequence, cordocentesis is often considered to evaluate fetal platelet count,[17–20] because, in TAR, platelet counts are often <50 platelets/nl (normal range 150–400 platelets/nl).[21] Although such a fetal platelet count is mandatory to establish the diagnosis of TAR syndrome and to differentiate it from other syndromes with malformations of the upper limbs, cordocentesis was reported to have a 1%–2% risk of fetal loss.[22] In addition, thrombocytopenia may not appear before the third trimester of pregnancy or even until the first months of life,[23] making an early diagnosis based on platelet count difficult.

To provide accurate genetic counseling, it is essential to make a correct diagnosis. In this case, we could utilize the very recent information about inheritance of TAR syn-

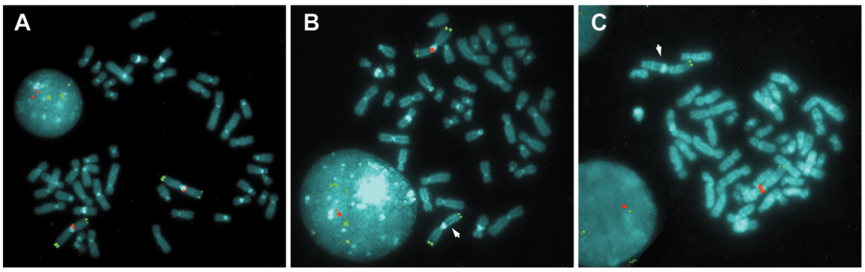

Figure 1. Hybridization patterns of BAC-clone RP11-698N18, which maps into the TAR microdeletion on chromosome band 1q21.1 on metaphase spreads of the mother (*A*), father (*B*), and fetus (*C*). Arrows in panels B and C indicate the derivative chromosome 1 with the microdeletion 1q21.1. *A,* In addition to BAC-clone RP11-698N18 (*red*), we hybridized BAC clones 14e10 (chromosome location: 1p36.3) and GS160H20 (1q44) (*both green*) as controls. In this exemplary metaphase spread, all probes show two signals each on the two chromosomes 1. Thus, the mother's karyotype can be described as: 46,XX.ish 1p36.3(14e10x2),1q21.1(RP11-698N18x2), 1q44(GS160H20x2). *B,* We hybridized the identical probe, set as described above, to the father's metaphase spreads. In contrast with our findings for the mother, we observed in all metaphase spreads only one hybridization signal for clone RP11-698N18. The father's karyotype is therefore 46,XY.ish 1p36.3(14e10x2),1q21.1(RP11-698N18x1),1q44(GS160H20x2). *C,* To metaphase spreads of the fetus, we hybridized, in addition to clone RP11-698N18 (*red*), only the 1p36 control probe 14e10 (*green*). There was again only one hybridization signal for clone RP11-698N18, indicating that the fetus had inherited the 1q21.1 microdeletion from his father. The complete karyotype of the fetus is 46,XY.ish 1p36.3(14e10x2),1q21.1(RP11-698N18x1).

drome,[14] and we offered the couple a prenatal diagnosis by amniocentesis. Conventional banding analysis showed a normal male karyotype (46,XY). However, in addition to conventional karyotyping, we now hybridized BAC-clone RP11-698N18, which maps into the TAR microdeletion on chromosome band 1q21.1[14] onto metaphase spreads of both parents and of the fetus. We observed two hybridization signals for the chromosome 1q21.1 clone on all analyzed metaphase spreads of the mother (fig. 1*A*), whereas all metaphase spreads of the father consistently showed only one signal (fig. 1*B*). In addition, we detected this 1q21.1 microdeletion in all metaphase spreads of the fetus (fig. 1*C*). The sonographic finding of upper-limb malformations in the fetus, together with the detection of the 1q21.1 microdeletion, allowed us to conclude from the aforementioned differential diagnoses that TAR syndrome is most likely. Therefore, we could provide precise genetic counseling, including a detailed explanation of the spectrum of phenotypic features associated with TAR syndrome. At a later date, the couple decided to terminate the pregnancy. Physical examination of the fetus revealed malformed upper extremities and absence of both radii, with opposable thumbs in an adducted position. The parents declined further examination, including a platelet count and a post mortem examination.

Our case nicely confirms the findings described by Klopocki et al.[14]—namely, identification of the interstitial microdeletion 1q21.1 in an unaffected parent and detection of the same microdeletion in an offspring with upper-limb deformities. As hypothesized elsewhere,[14] the TAR phenotype apparently develops only in the presence of an additional, as-yet-unknown modifier. It is likely that this modifier, in addition to the 1q21.1 microdeletion, was inherited not only in the current pregnancy but also in the previous, first pregnancy, which was, according to the clinical records, also associated with phocomelia.

Our case represents a prime example of the impact of newly gained, array-based knowledge on both genetic diagnostics and counseling. At present, utilization of this knowledge is in its early infancy. However, systematic collections of CNVs and their association with specific phenotypes in publicly accessible databases, such as DECIPHER (Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources) will certainly change our options in multiple counseling scenarios.

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Web Resources

The URLs for data presented herein are as follows:

DECIPHER, http://www.sanger.ac.uk/PostGenomics/decipher/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for 17q21.3 microdeletion syndrome, CHARGE syndrome, Pitt-Hopkins syndrome, Crohn disease, TAR syndrome, Holt-Oram syndrome, and Roberts syndrome)

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