Babu VR[1], Dev VG[2], Koduru P[3], Rao N[4] , Liu M[2], Fuentes E[1], Fuentes S[1], Papa S[1] and Van Dyke DL[5]

[1]InteGen LLC, Orlando, FL 32819; [2]Genetics Associates, Nashville, TN 37203; [3]UT Southwestern Medical Center, Dallas, TX 75390; [4]David Geffen UCLA School of Medicine, Los Angeles, CA 90024; [5]Mayo Clinic, Rochester, MN 55902

Interphase Chromosome Profiling (ICP): Development and validation of a novel technology and its clinical applications

To overcome the limitations of classical karyotyping, several molecular techniques (FISH, aCGH, SNP array, Next-Generation Sequencing) were introduced over the past 25 years. However, each of these along with the classical approach has its own drawbacks: long TAT, high failure rate, limited sensitivities, high expense, complicated interpretation, targeted approach, multiple reflex testing etc. Thus there is pressing need for a simpler, faster, failure-proof, more sensitive and cost-effective methodology for obtaining chromosomal results. We have developed and validated such technology in a multi-institutional study, termed Interphase Chromosome Profiling (ICP). Using an equidistant concept, selected FISH probes are chosen along the length of each chromosome arm such that chromosome gains, losses, and major rearrangements are detectable, matching a 600 band level karyotype analyses. However, unlike the GTG banding, in the ICP technique every band is molecularly distinct from every other band on that chromosome. Each chromosome is analyzed separately in interphase nuclei following the standard guidelines such as 20 cell analysis; the combined results produce a composite karyotype.

In a validation study, we demonstrated that for oncology specimens the ICP technique can detect clonal abnormalities as low as 5%. For the first time, we show in an interphase cell that a karyotype originally described as monosomy and a marker chromosome, is actually a derivative chromosome with a deletion. We further show that the ICP technique was able to refine the breakpoints and the size of deletions and duplications more precisely than the classical karyotype.

For POC, with a modified design with probes targeting only the subtelomere and centromere regions, we detected abnormalities common in POC tissues: tetraploid, triploid, aneuploid triploid, trisomy, double trisomy, monosomy, interstitial and terminal deletions, whole arm and partial duplications, and balanced as well as unbalanced Robertsonian translocations. The ICP technology and clinical applications will be discussed in detail.