Peripheral blood was received from a 16-year-old female patient for ovarian gonadoblastoma.

Submitted by:
Oregon Health & Science University
Knight Diagnostic Laboratories
Portland, Oregon

The answer to this Brain Tickler appears on pages 31-33.
The Journal of the Association of Genetic Technologists

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A while ago I received a package in the mail. It was from Linda Sheppard Howard, who was one of the first members of the Association of Cytogenetic Technologists (ACT), the forerunner of the AGT. The package contained a stack of Karyograms dating from about 1975 to about 1982. The Karyogram was the first newsletter of the ACT, and the early issues were essentially three or four typewritten pages stapled together. It was a little bit more focused on problem solving in the beginning. For instance, the September 1975 issue started with a Letter From Your Editor (Nancy K. Bergren), and a Helpful Hints column written by Associate Editor Patsy Wilkerson. The top of her Hints column was the use of Kodak SO 410 High-Contrast Copy film for their non-fluorescent photography.

I know. Some of you readers may not ever have used film in a camera. I can't tell you how old that makes me feel, but I was only 11 years old in 1975.

There were sections on techniques (Associate Editor Kathryn Wilson), Problem/Interesting Cases (Associate Editor Margaret Tyacy), Technical Problems (Associate Editor Marilyn Hack, who I believe is my friend Marilyn Arsham years before she became the editor of The Journal and before I ever met her), and so on.

Later on, apparently around 1982 or so, Karyogram became something resembling a technical journal with an ISSN number, a logo and real cover. The first article in Volume 8, Number 5, 1982 is by Ann C. Chandley and titled, “Effects of Radiation on Germ Cells and The Foetus.” Another article by Paul E. Bibbons, Jr. and Jack M. Rary is titled, “Histocompatibility-Y Antigen.” There is a Student-In-Training Review Article by Valerie Mary Lopes titled “Differential Cytogenetic Diagnosis in Chromosomal Breakage Syndromes.”

I also note that there is an ad on page 61 for Chang Medium (Chang C — Optimized Formula for Closed Culture Systems.) There are also some letters to the Editor “Trouble Shooting A Harvest Failure” and a Training column written by Helen Bixenman and Rodman Morgan and an update on the Technical Manual by the Chairperson of the Technical Manual Committee, Gitta Wahrenburg.

There are a few job postings as well, and, oh dear God…

Position Open: for a Cytogenetic Technologist to work in the area of Clinical Cytogenetics and help in research in basic Cytogenetics. Salary $14,000-$20,000.

Hmmm….

That job was for the Department of Biology at the University of Nevada in Reno. I also see a job posting in Dr. Ledbetter's lab at Baylor College of Medicine and several others.

I haven't decided quite what to do with these. Probably I will turn them over to the AGT Executive Office. It's possible some of these have already been imaged and are on the AGT website.

The note that came along with these said:

Iris Veomett & I (Linda Sheppard Howard) were among the first members. Since retiring in 2012, I've been sorting through my papers & found these old ACT journals. If they are of any use, please use them.

It was a wonderful time — being in the forefront of the technology. We often reminisce about the good old days.

Sincerely,
Linda

I think they're of use because the AGT, as it's now called, has played an important role over the last four decades in educating technologists involved in genetics on doing their jobs and perfecting the techniques that are still used today. I'm acutely aware that in my own 28 years or so around the world of genetics, things have changed. Maybe you remember that we didn't always know about imprinting. That we took it as gospel that because there were about 100,000 proteins, human beings had about 100,000 genes. But in the last decade or two we've discovered imprinting and that humans have about 15,000 to 20,000 genes and the entire field of epigenomics and new levels of nuance and complexity to how genetics actually works. They've changed how we do our jobs and how we look at the field of genetics. This continues today as new techniques come into play and more is learned. And with any luck, AGT will continue to be at the forefront of educating and informing the technologists who work in the field.

Cheers,
Mark Terry, Editor

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Multiple Copies of BCR/ABL Fusion Signals and t(3;21) in a Chronic Myeloid Leukemia: Patient with Blast Crisis – A Rare Event with Imatinib Mesylate (Gleevec)-Resistance in an Indian Patient

Manisha M. Brahmbhatt, Pina J. Trivedi, Dharmesh M. Patel, Shilin N. Shukla, Prabudas S. Patel

Abstract

Chronic myeloid leukaemia (CML) is characterized by the expression of BCR/ABL fusion gene, a constitutively activated tyrosine kinase that commonly results from the formation of the Philadelphia (Ph) chromosome after a t(9;22)(q34;q11) or variant rearrangement. The duplication of Ph chromosome is a recurring abnormality acquired during disease progression, whereas intrachromosomal amplification of BCR/ABL is a rare phenomenon and has been associated with imatinib mesylate (IM) therapy resistance. In the present study, we used G-banding to identify the presence of identical isochromosomes of the Ph chromosome and t(3;21)(q26;q22) resulted from clonal evolution in IM-resistant patient. Fluorescence in situ hybridization (FISH) using dual color dual fusion probe analysis on interphase and metaphase nuclei confirmed the amplification of the fused BCR/ABL gene. Our study indicated that the progenitor of CML was BCR/ABL dependent through the amplification of Ph chromosome as a mechanism of resistance to IM therapy. The coexistence of BCR/ABL and t(3;21)(q26;q22) with RUNX1 rearrangement might play a pivotal role in the CML blast transformation.

Introduction

Chronic myeloid leukaemia (CML) is a malignant pluripotent haematopoietic stem cell disease characterized by the expression of the BCR/ABL fusion gene. It is a constitutively activated tyrosine kinase that commonly results from the formation of the Philadelphia chromosome (Ph) after a t(9;22)(q34;q11) or related variant rearrangement (Melo and Barnes, 2007). Amplification of BCR/ABL, as well as mutations of the fusion gene, has been shown to be associated with clinical resistance to imatinib mesylate (IM) therapy (Gorre et al., 2001; Hochhaus et al., 2002). The blast phase of CML is characterized by acquisition of new cytogenetic abnormalities in 80% of CML patients, the most common being trisomy 8, duplication of the Ph chromosome and isochromosome 17, and a rare recurring translocation, t(3;21)(q26;q22) (Phan et al., 2008; Quintas-Cardama and Cortes, 2009). The RUNX1/ EVII (previously AML1/EVII) transcription factor generated by the t(3;21)(q26;q22) translocation plays a pivotal role in leukemogenesis of advanced CML. This t(3;21) is also found in patients with therapy-related myelodysplastic syndrome (t-MDS) and therapy-related acute myeloid leukaemia (t-AML) (Phan et al., 2008). The additional Ph chromosome houses a second copy of the BCR/ABL fusion resulting in genomic amplification of the chimeric gene. In addition, extra copies of the fusion gene have also been described housed by isochromosomes derived from the Ph chromosome or marker structures containing tandem duplications of BCR/ABL fusion (Campbell et al., 2002; Gangallo et al., 2003; Phan et al., 2008; Szych et al., 2007).

The IM therapy is highly effective for CML. It results in a complete cytogenetic response in 87% of patients with newly diagnosed chronic-phase CML (O’Brien et al., 2003). Complete hematologic responses with IM therapy have been seen in 95% of patients in chronic phase CML after failure of interferon-a, 71% of accelerated phase patients, and 31% of patients in myeloid blast crisis (Kantarjian et al., 2002; Sawyers et al., 2002; Talpaz et al., 2002). However, drug resistance to IM has been reported in the past few years. The resistance can be primary or secondary (after an initial response). Both the types of resistance occur most frequently in the blast crisis phase of CML (Hochhaus and Hughes, 2004; Litzow, 2006). Multiple mechanisms of resistance to IM have been described. Resistance may occur as a result of increased expression of the BCR/ABL kinase from genomic amplification, clonal chromosomal evolution, or mutations in the ABL kinase of the BCR/ABL gene affecting drug interaction or kinase activity (Hochhaus et al., 2002).

In the present study, we report a case with rearrangement of the Ph chromosome involving gains of the fusion gene. Apart from the duplication of the entire Ph chromosome, we identified the presence of one, two or three isoderivative chromosome 22 [ider(22)t(9;22)] and t(3;21)(q26;q22). This is the first report from India that documents the instability of the Philadelphia chromosome, due to formation of isoderivative Ph and t(3;21) (q26;q22) establishing genomic instability resulting in increased secondary resistance to IM therapy.

Materials and Methods

Case Report

A 44-year-old CML male was diagnosed in August 2010. At diagnosis, the blood examination revealed hemoglobin (Hb) level of 106 g/L, white blood cell (WBC) count of 234 x 10^9/L, platelet count 354 x 10^9/L. The bone marrow trephine biopsy revealed hypercellular marrow and normoblastic erythropoiesis. Myeloid to erythroid ratio was 15:1. Increased megakaryocytes were seen and findings were suggestive of CML-Chronic Phase (CP). Reverse-transcriptase polymerase chain reaction confirmed the presence of the BCR/ABL fusion, resulting in the 210-kDa BCR/ABL transcript in March 2011 and May 2011.

In May 2011, blood examination indicated Hb level of 130 g/L, WBC count of 12.9 x 10^9/L, platelet count 91 x 10^9/L. The repeat bone marrow aspiration (October 2011) indicated mild hypercellular marrow. Myeloid to erythroid ratio was 4.4:1. Megakaryocytes were seen and findings were suggestive of CML-CP.

During the last follow-up in April 2012, blood examination indicated Hb level of 104 g/L, WBC count of 178.8 x 10^9/L, platelet count 224 x 10^9/L and bone marrow aspiration revealed chronic myeloid leukemia—blast crisis (myeloblastic).

From September 2010, the patient was treated with imatinib mesylate (400 mg/day, Gleevec; Novartis, East Hanover, NJ). The dose was increased due to loss of complete hematologic remission to 600 mg/day from November 2011, and then further increased...
Multiple Copies of BCR/ABL Fusion Signals and t(3;21) in a Chronic Myeloid Leukemia: Patient with Blast Crisis – Brahmbhatt, Trivedi, Patel, Shukla, Patel

to 800 mg/day from April 2012. The patient has yet to achieve a hematologic or cytogenetic response.

Conventional Cytogenetics and FISH

Short-term culture of bone marrow cell harvesting and GTG banding was performed according to standard procedures following karyotyping according to ISCN 1995 guidelines (Shaffer et al., 2009; Verma and Babu, 2009). Locus Specific Identifier (LSI) probes for BCR/ABL gene rearrangement, dual color dual fusion (DCDF), BCR/ABL-ES (Extra Signal), BCR/ABL-Tricolor, LSI-DCDF-AML-ETO and whole chromosome paint (WCP) for chromosome 21 spectrum orange (SO) were performed (Abbott Molecular-Vysis, Des Plaines, IL) according to the manufacturer’s protocols.

Results

Conventional Cytogenetics

The conventional cytogenetic report in September 2010 was 46,XY,t(9;22)(q34;q11)[20]. The karyotype result in October 2011 was 46,XY,der(9)t(9;22)(q34;q11.2),ider(22)t(9;22)(q34;q11.2),add(21q)[10]/46,XY,t(9;22)(q34;q11.2),add(21q)[5]. In April 2012, it was 47,XY,der(9)t(9;22)(q34;q11.2),ider(22)t(9;22)(q34;q11.2),+ider(22)t(9;22)(q34;q11.2)add(21q)[4]/46,XY,der(9)t(9;22)(q34;q11.2),ider(22)t(9;22)(q34;q11.2),add(21q)[5]. One to three copies of the isoderivative 22 were identified, indicating the presence of duplication/amplification of the Philadelphia chromosome.

FISH

Gains of the Ph chromosome taking the form of an ider(22) t(9;22)(q34;q11) chromosome were detected on metaphase FISH, which identified the cell populations with an isoderivative chromosome 22, ider(22)t(9;22)(q34;q11).

BCR-ABL-DCDF

In October 2011, the FISH for BCR/ABL DCDF probe results indicated 54% cells with typical positive signal pattern; 1R1G2F (Fig. 1A) and 46% cells showed 1R1G3F, indicated an ider(22) on metaphases and interphases (Fig. 1B).

During follow-up in April 2012, the FISH using BCR/ABL DCDF probe revealed: 8% cells with typical positive signal pattern 1R1G2F; 13% cells showed 1R1G3F, indicating an ider(22) (Fig. 1B); 54% cells showed 1R1G5F (Fig. 1C), and indicated two copies of ider(22); and 25% cells showed 1R1G7F, which indicated three copies of ider(22).

BCR/ABL-ES

The FISH for BCR/ABL-ES probe results confirmed the presence of ider(22)t(9;22)(q34;q11).

BCR/ABL-Tricolor

The FISH results for BCR/ABL-Tricolor probe confirmed the presence of ider(22)t(9;22)(q34;q11) as well as no deletion on der(9), as both the aqua signals for ASS gene were observed on der(9).

Detection of t(3;21)(q26;q22)

LSI-DCDF FISH AML1/ETO

Using a LSI-DCDF FISH AML1/ETO probe for RUNX1/ RUNXI, no evidence of the fusion gene was observed. The red ETO signal for the RUNXI gene indicated normal signals on the long arms of both chromosomes 8. Three green AML1 signals for the RUNXI gene were located on the long arm of derivative chromosome 3, the derivative chromosome 21, and the normal chromosome 21. The metaphase FISH results confirmed and identified the t(3;21)(q26;q22).

WCP 21

The additional chromosomal material on der(21q) was confirmed by WCP 21. The WCP 21 showed three orange signals; one signal for normal chromosome 21, one orange signal on der(21), and one orange signal on der(3). The metaphase FISH results have confirmed and disclosed the t(3;21)(q26;q22).

Discussion

The leukemogenesis of CML is a multistep process that involves multiple genetic abnormalities. BCR/ABL, the causative molecular abnormality, is essential for the induction and maintenance of CML. Progression of CML with cytogenetically abnormal clones remains throughout the course of the disease, accompanied by secondary chromosomal abnormalities often indicating increased aggressiveness of disease, and precede clinical manifestations of blast crisis. Although CML patients can be treated effectively with IM, a potent selective inhibitor of tyrosine kinase ABL transcript, a subset of patients nonetheless lose their response to IM. This occurs mainly in patients progressing to the accelerated phase or in blast phase of CML. Two broad categories of mechanisms have been implicated in IM failure: primary and secondary resistance. Primary resistance is defined as an inability to achieve good response to treatment in the initial stage. Secondary or acquired resistance arises in patients who initially achieve response but subsequently lose relevant response even after extended period of medication (Phan et al., 2008).

Although intrachromosomal amplification of BCR/ABL is a rare phenomenon, the duplication of the Ph chromosome resulting in two copies of the BCR/ABL fusion gene is a common abnormality acquired during CML disease progression, although it can be observed during the chronic phase as well. The presence of multiple copies of the isoderivative Ph chromosome is a rare rearrangement that has been previously described (Pernice et al., 1993; Virgili and Nacheva, 2010). Cytogenetic studies often provide evidence of progression of disease at an earlier phase than hematologic markers. It is known that expression of BCR/ABL is elevated in progenitor cells in blast crisis, compared to chronic-phase CML (Barnes et al., 2005). While the findings of the patient’s peripheral blood and bone marrow were suggestive of CML in the chronic phase, given the presence of the ider Ph chromosome and t(3;21)(q26;q22), it may be possible that cytogenetics indicated progression of the disease toward an accelerated phase. The presence of multiple copies of the BCR/ABL oncogene is indicative of a poor prognosis and higher possibilities for resistance to drug treatment (Coutre et al., 2000).
Multiple Copies of BCR/ABL Fusion Signals and t(3;21) in a Chronic Myeloid Leukemia: Patient with Blast Crisis – Brahmbhatt, Trivedi, Patel, Shukla, Patel

A. BCR/ABL-DCDF: 1R1G2F  

B. BCR/ABL-DCDF: 1R1G3F  

C. BCR/ABL-DCDF: 1R1G5F  

E. BCR/ABL-ES: 2R1G4F  

F. BCR/ABL-Tricolor: 1RAq1G1RGAg4F  

G. AML1/ETO-DCDF: 2R3G
Case Study

Multiple Copies of BCR/ABL Fusion Signals and t(3;21) in a Chronic Myeloid Leukemia: Patient with Blast Crisis – Brahmmbhat, Trivedi, Patel, Shukla, Patel

Figure 1 FISH results

Figure legends:

A. **BCR/ABL-DCDF**: 1R1G2F; a metaphase showing typical positive signal pattern for *BCR/ABL* fusion.

B. **BCR/ABL-DCDF**: 1R1G3F; a metaphase showing variant positive signal pattern for *BCR/ABL* fusion, indicating one copy of ider(22)t(9;22)(q34;q11.2).

C. **BCR/ABL-DCDF**: 1R1G5F; a metaphase showing variant positive signal pattern for *BCR/ABL* fusion, indicating two copies of ider(22)t(9;22)(q34;q11.2).

D. **BCR/ABL-DCDF**: 1R1G7F; a metaphase showing variant positive signal pattern for *BCR/ABL* fusion, indicating three copies of ider(22)t(9;22)(q34;q11.2).

E. **BCR/ABL-ES**: 2R1G4F; a metaphase showing variant positive signal pattern for *BCR/ABL* fusion, indicating two copies of ider(22)t(9;22)(q34;q11.2).

F. **BCR/ABL-Tricolor**: 1RAq1G1RGAq4F; a metaphase showing variant positive signal pattern for *BCR/ABL* fusion, indicating two copies of ider(22)t(9;22)(q34;q11.2).

G. **AML1/ETO-DCDF**: 2R3G; a metaphase showing 2 red signals of *ETO* gene on chromosome 8 and 3 green signals of *AML* gene, i.e., 1 green signal on normal chromosome 21, one split green signal on derivative chromosome 21 and another green signal on derivative chromosome 3.

H. **WCP21**: 3G; a metaphase showing WCP 21 results, one green signal is on normal chromosome 21, one green signal is on der(21) and another green signal is on der(3).
Multiple Copies of BCR/ABL Fusion Signals and t(3;21) in a Chronic Myeloid Leukemia: Patient with Blast Crisis – Brahmbhatt, Trivedi, Patel, Shukla, Patel

FISH using the LSI BCR/ABL DCDF and ES Dual Color translocation probe was helpful in refining the characterization of the ider Ph chromosome by demonstrating the presence of two fusion signals within the rearrangement. Not only did it pick up the clones seen by routine cytogenetics with one to three copies of the ider Ph chromosome (67%), but also detected the presence of cells with three copies of the ider Ph chromosome (25%) (Fig. 1B), resulting in multiple copies of the BCR/ABL fusion oncogene. In addition, we have prioritized observations from metaphase chromosomes, whereas most studies depended on only interphase FISH analysis.

Reports of ider Ph chromosomes in CML have been infrequent; in the present case, it was clonal evolution from a sole Ph chromosome to ider Ph chromosome. The patient failed to respond to treatment with Gleevec, and subsequent analysis showed multiple copies of ider Ph chromosomes. The presence of multiple gene copies of the BCR/ABL oncogene seems to be the cause for the ineffectiveness or resistance to the drug, despite increased drug dosage (Coutre et al., 2000).

The causative factor in the formation of the ider Ph chromosome is unknown. ider Ph chromosome may lead to breakage and reunion cycles during mitosis potentially forming isochromosomes and thus leading to genomic instability and heterogeneity in the cell population. Furthermore, these ider Ph chromosomes can be heterogeneous in copy number, which lead to amplification and duplication of the hybrid BCR/ABL genes on the ider Ph chromosome. Gene amplification and genomic heterogeneity are known to be associated with drug resistance (Barnes et al., 2005; Bubnoff et al., 2003; Campbell et al., 2002; Gorre et al., 2001; Hochhaus et al., 2002). Therefore, formation of the ider Ph chromosomes may play a crucial role in the amplification and heterogeneity of the BCR/ABL gene, which lead to drug resistance to IM therapy for CML patients.

The occurrence of a t(3;21) translocation together with amplification of BCR/ABL marks the aggressiveness of disease progression. The cooperation of both oncogenic RUNXI and EVII resulting from t(3;21) translocation with BCR/ABL in blocking myeloid differentiation causes the rapid induction of myelogenous leukemia in cases with imatinib-resistant CML. We could speculate that this aberrant chromosome plays a critical role in initiating blastic transformation of CML and confers treatment resistance by allowing the selection or genesis of resistance clones. It is possible that such cooperation of these hybrid genes can interfere with imatinib binding and promote the Ph-positive resistant clones that eventually constitute the bulk of the population (Phan et al., 2008). The problem of gene amplification and genomic instability may be overcome by administering higher doses of IM to patients who develop this subcategory of IM resistance. If, however, IM is implicated in the etiology of the chromosomal breakpoints, inducing nonrandom breakpoints at the subtelomere or telomere region of the Ph chromosomes, other therapies must be sought. Elucidation of these specific disease mechanisms may help yield additional therapies to even be co-administered with IM. Two such drugs are dasatinib and nilotinib (Walz and Sattler, 2006).

To the best of our knowledge, this is the first case report of blastic myeloid transformation of CML with ider(22) and RUNXI disruption. BCR/ABL is, we believe, an essential feature for induction and maintenance of the malignant phenotype of CML. A few strategies have been proposed to obviate the development of imatinib resistance, such as designing additional kinase inhibitors to be given along with imatinib or modulation of the imatinib doses. In the meantime, allogeneic bone marrow or stem cell transplant remains an option, offering possible long-term remission for CML. The exact role of t(3;21) in the pathogenesis of CML is unclear, and occurrence of t(3;21) at any phase of CML could be an important marker correlated with the involvement of a more aggressive progression of CML, as well as with the possible emergence of resistant cells. Determining the role of these chromosomal aberrations and genetic defects may allow for more rational therapeutic approaches, designed to improve outcome for patients with a poor prognosis (Phan et al., 2008). More studies with larger cohorts must be conducted regarding IM resistance and the development of ider Ph chromosome and t(3;21). Certainly, early cytogenetic detection of ider Ph chromosome in CML patients will lead to improved interventions and outcomes in future CML patients.

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Case Study

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Acute Myeloid Leukemia with a Masked Type of Three-Way t(8;11;21) Revealed by Fluorescence In Situ Hybridizations Using AML1-ETO Probe

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Abstract

The translocation (8;21)(q22;q22) is a recurrent aberration in AML, preferentially appearing in the French American British (FAB) classification M2 subtype. The accurate detection of this chromosomal rearrangement is vital due to its association with a favorable prognosis. Variants of t(8;21)(q22;q22) involving chromosomes 8, 21 and other chromosomes account for approximately 3% of all (8;21)(q22;q22) in AML. Variants in some cases present as hidden translocations, and in such cases it is often difficult to confirm the presence of t(8;21)(q22;q22) by conventional cytogenetic analysis alone. The molecular detection of the AML1-ETO fusion gene is possible by reverse transcriptase polymerase chain reaction (RT-PCR) or dual-color fluorescence in situ hybridization (FISH) using probes specific for AML1 and ETO. The mechanism described for variant formation is one step or two steps.

We report a case of AML with a masked variant translocation. Conventional cytogenetics and FISH study was carried out on a bone marrow sample of the patient at diagnosis. Karyotype result at diagnosis revealed t(8;11)(q22;p15) by G-banding. FISH analysis disclosed a 3-way translocation involving chromosomes 8, 11, and 21 and identified a masked variant t(8;21)(q22;q22) using AML1-ETO probe and whole chromosome paint probes (WCP) 8 and 11 with a one-step mechanism.

FISH analysis with the AML1 and ETO probes is extremely valuable in cases of AML-M2 because of its ability to reveal masked t(8;21)(q22;q22) translocations and thus quickly confirm the diagnosis, allowing patients to be assigned to the correct risk group in terms of treatment. Simple variants of the t(8;21) translocation involving chromosome 8 and a chromosome other than number 21 are rare. Our case illustrates the challenge of recognizing complex aberrations that occur with variant t(8;21) and further reinforces the utility of FISH applications on metaphase for more accurate characterization of chromosome abnormalities which can lead to more precise therapeutic stratification.

Introduction

The translocation t(8;21)(q22;q22) is a recurrent aberration in AML, preferentially appearing in the French American British (FAB) classification M2 subtype and less frequently in M1 or M4. In childhood AML this aberration is the most prevalent karyotypic anomaly, with an incidence of about 12% (Rowley, 1973; Vundinti et al., 2008). The translocation leads to the fusion of the AML1 and ETO genes on the derivative chromosome 8 [der(8)], and patients positive for the chimeric gene are known to have a favorable prognosis (Grimwade et al., 2001). Therefore, the translocation is highly important for diagnosis and treatment choice.

In addition to the classical t(8;21), rearrangements involving 8q22, 21q22, and chromosomes of variable origin have been reported in adult as well as in childhood leukemia (Gallego et al., 1994; Saitoh et al., 1997; Vieira et al., 2001). Approximately 3% of cases with t(8;21) showed a complex variant involving chromosomes 8, 21, and a third or fourth chromosome (Xue et al., 2000). In general, morphological and clinical differences between these variants and t(8;21) have not been detected with conventional cytogenetics alone (Keiki et al., 2008).

The t(8;21) or the AML1-ETO rearrangement can be identified by conventional cytogenetics, FISH or RT-PCR (Gamerdinger et al., 2003). Conventional cytogenetics, on the other hand, may overlook the rearrangement in patients with hidden aberrations. To obtain as much genetic information about the leukemic cells as possible, classical cytogenetics as well as a combined approach of FISH assay should be performed for further characterization.

Here, we describe a three-way t(8;11;21)(q22;p15;q22) in a patient with AML identified with conventional and molecular cytogenetics.

Materials and Methods

Case Details

A 42-year-old female visited our institute in the first week of January 2012, with chief complaints of generalised weakness, low grade fever, vomiting, and headache. Laboratory investigations revealed hemoglobin 7.8 gm/dl, white blood cell (WBC) 2600/mm³, and platelets 11,000/mm³. Differential WBC counts showed polymorphs 44%, lymphocytes 32.2%, monocytes 1.4%, eosinophils 1.9%, and basophils 0.5%. Bone marrow report showed normocellular bone marrow aspirate smear with 31% blasts cells. Blast cells were medium to large in size with fine chromatin, 0-2 prominent nucleoli and scant to moderate amount of cytoplasm. Few showed cytoplasmic granulation. Erythroid precursors were relatively suppressed. Erythropoiesis was normoblastic, M:E ratio was altered. Megakaryocytes were not observed. Peripheral smear showed leucopenia with 2% blast cells and severe thrombocytopenia was present. Final diagnosis was acute leukemia morphologically myeloblastic.

Flow cytometry immunophenotyping was performed on bone marrow and demonstrated a predominance of myeloid cells with percent positivity for the CD 13 (50%), CD 117 (33%), MPO (64%), CD 34 (48%), HLADR (34%), Tdt (3%). In bone marrow, 31% blasts were gated using CD45 Per CP vs. Side scatter. The blasts mainly expressed myeloid markers MPO, CD13 and CD117 along with CD34 and HLADR. The final diagnosis was AML. The blasts were negative for the markers CD 19 (00%), CD 79a (00%), CD 5 (00%), CD 7 (00%), CD 22 (00%), CD 3 (02%), CD 10 (00%), and CD 33 (13%).

Cytogenetic Analysis

Chromosome preparation from bone marrow and peripheral blood was performed by standard protocol after culturing for 48
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Fig. 1. G banded karyotype results showing t(8;11)(q22;p15).

Fig. 2. FISH using LSI AML1-ETO dual color dual fusion probes. Results showed signal pattern was 2O2G1F. One AML1-ETO Fusion on der(8), one orange signal on normal chromosome 8 and one orange signal on der(11)(p). Out of two green signals one green signal on der 22 and one green signal on normal 22.

Fig. 3. WCP FISH probes for chromosome 8 Spectrum Orange and chromosome 11 Spectrum Green. FISH results confirmed t(8;11)(q22;p15).
hours. Metaphase spreads were prepared by use of routine methods, including colcemid treatment, hypotonic shock, and 3:1 methanol/ acetic acid fixation, and chromosome analysis was carried out on G-banded metaphase cells (Verma and Babu, 1995). In general, at least 20 metaphases were karyotyped and described according to the International System for Human Cytogenetic Nomenclature (ISCN, 2009) (Shaffer et al., 2009).

**FISH Study Using Different Probes**

FISH analysis was performed on bone marrow aspirate with the following probes (Abbott Molecular, Des Plaines, IL), according to the manufacturer’s instructions: for identification of AML1-ETO fusion, locus-specific identifier (LSI) dual-color dual-fusion AML1-ETO probe was applied. Whole chromosome paint probes for WCP 8 with spectrum orange and WCP 11 with spectrum green were also applied.

**Results**

**Cytogenetic Analysis**

At first, G-band analysis of bone marrow cells showed 46,XX,t(8;11)(q22;p15) in all of the 20 metaphase cells analyzed (Fig. 1).

**FISH Analysis**

FISH analysis for the AML1-ETO probe showed signal pattern 2O2G1F; the AML1-ETO fusion signal was present on the chromosome der(8) (Fig. 2). Two green signals of ETO gene were present, one on a normal chromosome 21 and the other on the derivative 21, respectively. One orange signal of the AML1 gene, which should be present on der(21), was instead observed on der(11p). Hence, results of the LSI AML1-ETO probe confirmed a three-way translocation between three different chromosomes, i.e., 8, 11, and 21. WCP FISH for chromosome 8 and 11 also confirmed a translocation between the long arm of chromosome 8 and the short arm of chromosome 11 (Fig. 3).

**Final Diagnosis**

However, from chromosomal breakpoints of 8q22 and 11p15, the possibility of a masked type translocation for t(8;21)(q22;q22) was raised. FISH analysis was carried out using different LSI and WCP probes. The karyotype was finally determined as 46,XX,der(8) t(8;11;21)(q22;p15;q22)[20]. The karyotype was described according to the ISCN (2009). These results indicated the presence of a three-way translocation involving chromosomes 8, 11, and 21.

**Discussion**

Translocation (8;21)(q22;q22) is a frequent karyotypic abnormality in AML-M2, which is easily identifiable by standard cytogenetic analysis. The observation of an AML1 rearrangement or of AML1-ETO fusion transcripts detected by Southern blot or RT-PCR analysis, respectively, in patients without cytogenetic evidence of a classical t(8;21) indicated that the AML1-ETO fusion gene could result from a variant or masked chromosomal rearrangement involving chromosome 8 and 21. To date, variants of t(9;22) were observed in 5% of cases in chronic myeloid leukemia (CML) (Brahmbhatt et al., 2010), whereas, in AML, variants of t(8;21) were observed in 3-4% of cases involving chromosomes 1, 2, 4, 5, 6, 7, 8, 10, 12, 13, 15, 17, 18, 19 or 20 (Kokate et al., 2008). In the present study, we have described a three-way translocation, t(8;11;21)(q22;p15;q22), identified in an AML patient. In many instances, three-way translocations involving 11p15 are not only difficult to detect, but also difficult to interpret with cytogenetic means alone, although the classical translocation and its variants are well documented.
11p15 rearrangements are observed in 3% of t-MDS/t-AML and have been reported in 5% of childhood t-MDS/t-AML and 53% in hematologic malignancy. The NUP98 gene is located on 11p15 and is a component of the nuclear pore complex implicated in nucleocytoplasmic transport and involved in different types of AML. A total of 29 different partners and translocations of NUP98 gene were observed to date as fusion with t(1;11)(q23;p15)(PMXI-NUP98), t(2;11)(q31;p15)(HOXD13-NUP98), t(4;11)(q22;p15) (NUP98-RAPIDGDS1), t(7;11)(p15;p15) (HOX9-NUP98), t(9;11) (p22;p15)(NUP98-LEDGF), inv(11)(p15;q22) (NUP98-DDX10), t(11;20)(p15;q11) (NUP98-TOP1) (Viguie, 2002). Other genes present on the same region, i.e., 11p15, are LIM domain only 2 (rhombotin-like 1), (LMO). LMO2 and TAL1 are able to partially suppress myeloid differentiation. This region may harbour a critical candidate gene that plays a role in the pathogenesis of AML (Cuneo, 2002). Translocation of the 11p gene with different chromosomes such as 3, 4, 6, 7, 8, 9, 10, 12, 14, 15, 16, 17, 19, 20, 21 and 22 were observed in different leukemias. To date, t(8;11;21) was observed in a total of two AML cases, and were reported with t(8;11;21). In the current study, it was a rare and masked t(8;11;21) (Mitelman et al., 2013).

Up to 2008, there were 60 different cases observed with variants of AML1-ETO involving a third chromosome (Kokate et al., 2008). In CML, there are different mechanisms for variant formation, i.e., one-step and two-step. The mechanism involved in this rearrangement is a one-step mechanism in which the chimeric AML-ETO gene was first developed on der(8) and subsequently translocated to 11p15 (Fig. 4). Mechanisms behind formation of complex or variant translocations highlight the importance of the AML1-ETO fusion transcripts in pathogenesis of the leukemia (Ahmad et al., 2008).

Furthermore, a dual-color FISH method with locus-specific probes revealed the colocalization of AML1 and ETO signals on the rearranged chromosome at q22. FISH results were established to identify the AML1-ETO fusion and was recommended for application in interphase and metaphase diagnostics of minimal residual disease or in clonality studies (Hagemeijer et al., 1998; Sacchi et al., 1995). These probes also make it possible to detect the gene fusion in nonclassical or masked translocations (Harrison et al., 1999; Tabiaux et al., 1999). Also, Xue et al. (2001) described a complex three-way rearrangement, t(8;21;8)(p23;q22;q22), combining conventional karyotype, FISH or RT-PCR analyses, which is a rational strategy for identification of the complex variants of t(8;21) translocation.

The current case, along with other cases from the literature presenting variant chromosome translocations, strengthens the relevant role of the der(8) chromosome, which carries the AML1-ETO fusion protein in the pathogenesis of AML-M2. This study also emphasized the role of metaphase FISH in searching for colocalization of AML1-ETO fusion. AML patients with t(8;21) variants are included within a subgroup of AML-M2 patients who are considered to have a high remission rate and prolonged disease free survival when treated with standard induction and consolidation chemotherapy. These studies should be followed up for longer duration to determine the significance of such variants to assess the prognosis in terms of therapy outcome.

Conclusion

In conclusion, our investigation indicated that a number of cytogenetically cryptic abnormalities leading to an AML1-ETO fusion may be missed without investigation at the molecular cytogenetic level, because they were beyond the limitations of conventional cytogenetics. The AML karyotypes with variant aberrations involving either 8q22 or 21q22 may also carry an AML1-ETO fusion caused by mechanisms other than classical translocation and should be reevaluated by molecular methods.

In addition, two independently performed techniques can confirm the results and minimize the risk of false positive or negative results by either method. The routine analysis of AML patients with the combination of classical cytogenetics and molecular methods like PCR and/or interphase and metaphase FISH will allow better stratification for all AML patients. The analysis of AML bone marrow samples by more than one technique will also clarify the true incidence of cryptic variant leukemia-specific chromosome rearrangements, thereby providing a more detailed insight into the mechanisms creating fusion genes. The additional reports on clinical features of these types of variants are needed to improve our understanding of the biology and pathogenesis of the M2 subtype of AML.

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Seizure Disorder in a Patient with a 5.09 Mb 7q11.23-q21.11 Microdeletion Including the MAGI2 Gene

Jess F. Peterson, Pankaj Thakur, Abigail Peffer, Marta Kolthoff, Sally J. Kochmar, Urvashi Surti

Abstract

Infantile spasms (IS) are a severe form of epilepsy characterized by hysparrhythmia on EEG, spasms, and intellectual disability. Typically occurring before one year of age, 40-60% of patients diagnosed with IS eventually develop other seizure disorders later in life. The etiology of IS is broad, and only recently have IS-associated genes been identified. MAGI2, an implicated IS-associated gene located within the 7q11.23-q21.11 chromosome region, encodes for a synaptic scaffolding protein involved in synaptic development and function. To date, several case reports of patients with 7q11.23-q21.11 microdeletions involving MAGI2 have been described, with the majority presenting with IS or other seizure disorders that are attributed to loss of heterozygosity of the MAGI2 gene. In addition, several other patients with 7q11.23 microdeletions not including MAGI2 have been described with clinical features that include IS, epilepsy, intellectual disabilities, and neurobehavioral problems, raising the possibility of additional candidate genes located within the 7q11.23 region. Adding to the literature, we report on a 21-year-old female with a de novo 5.09 Mb 7q11.23-q21.11 microdeletion (aCGH analysis) involving the MAGI2 gene with a history of seizure disorder, intellectual disability, and dysmorphic features. Although we agree that MAGI2 is the most likely candidate gene for seizure disorder in our patient, other candidate genes must be considered in 7q11.23 deletion cases not spanning the MAGI2 gene.

Key Words: 7q11.23-q21.22; 7q11.21-q11.23; 7q11.23; infantile spasms; seizure disorders; MAGI2; MAGI2 imprinting; HIP1; array comparative genomic hybridization (aCGH)

Introduction

Infantile spasms (IS) are a severe form of epilepsy that develop in early infancy with features that typically include myoclonic-tonic seizures, hysparrhythmia pattern on EEG, and psychomotor delay/arrest (Wheless et al., 2012). In addition, other seizure types are reported in up to 60% of children with IS even after cessation of spasms (Wheless et al., 2012). Although the etiology of IS can be attributed to prenatal, perinatal, and postnatal causes, the genetic basis has become more evident with the discovery of mutations and copy number variants that are linked to IS-associated genes (Lux et al., 2013; Paciorkowski et al., 2011; Tiwari et al., 2012). Located within chromosome region 7q11.23-q21.11 is MAGI2, an IS-associated gene which encodes a protein that plays a direct role in synaptic development and function (Paciorkowski et al., 2011).

To date, a total of 16 patients have been reported in the literature to have 7q11.23-q21.11 microdeletions that include or disrupt the MAGI2 gene, with 15 of these patients reported to have IS (Marshall et al., 2008). Of these 16 patients, 10 also had microdeletions that included the Williams-Beuren syndrome critical region (WBSCR), which is located approximately 4 Mb centromeric to the MAGI2 gene. Deletions of the MAGI2 gene in these patients have resulted in clinical phenotypes that include IS or other seizure disorders, intellectual disability, dysmorphisms, and Williams-Beuren syndrome (if deletions span the WBSCR) (Marshall et al., 2008). However, IS and other seizure disorders have been reported in 7q11.21-q11.23 deletion cases that did not include the MAGI2 gene (Marshall et al., 2008; Ramocki et al., 2010; Röthlisberger et al., 2010), raising the possibility of additional candidate genes located within the deleted 7q11.21-q11.23 chromosome region.

Adding to the literature, we report on a 21-year-old female with seizure disorder, intellectual disability, and dysmorphic features who was discovered by aCGH analysis to carry a de novo 5.09 Mb deletion of the 7q11.23-q21.11 chromosome region that included the MAGI2 gene.

Clinical Report

The patient is a 21-year-old Caucasian female who has been followed by our Center for Medical Genetics for 19 years. She was born at full term to an 18-year-old, G1P0 mother after an uncomplicated antenatal course and weighed 3004 g (23rd centile). The patient was evaluated for early intervention services at the age of 20 months following parental concerns for developmental delay. She sat alone at eight months and walked by 16 months. At time of examination, her gross motor skills were at 14-16 months range and fine motor skills at the level of 15 months. Neuropsychological assessment placed her at low borderline range and at risk for developmental and intellectual disability (Vineland Adaptive Behavior Scale score: 74). Although appropriate weight for age, she had feeding problems secondary to reflux and chronic constipation through one year of age. She was also found to have right esotropia for which she wears corrective glasses.

We first evaluated the patient in 1994 for global developmental delay at 32 months of age. At our initial assessment her weight was 17 kg (>95th centile), height was 92.1 cm (50th centile) and head circumference was 50.5 cm (>90th centile). She demonstrated the following dysmorphic features: round face, thin upper lip, small anteverted nose, prominent blue eyes, short foot length (<5th centile), short hand length (<5th centile) and fifth finger brachydactyly. At that time, she underwent routine chromosome studies and Fragile X testing. Karyotype was established at 500 G-band resolution and appeared to be normal, with inverted chromosome 9: 46,XX.inv(9)(p11q13). Parents were counseled about the normal inv(9) variant occurring in 2% of population with no associated pathology. Her initial Fragile X studies revealed normal FMR1 allele with 30 CGG repeats.
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Fig. 1. Pictures of our patient aged 20 years. A, B) Note the fine hair, high anterior hair line, large forehead, blue eyes, long smooth philtrum and thin upper lip, small anteverted nose, right esotropia, and long eyelashes. C, D) Our patient’s hands are small in size with a short fifth digit and proximally placed thumbs. Note the hypoplastic nails with hypoplastic distal phalanges.

The patient was reevaluated in 2004 at age 12 years. Her interval history was significant for an IQ in the mental retardation range, tics and seizure disorder. She was being treated with Buspar, Prozac and Depakote. On examination her head circumference was 54 cm (>90th centile), height was 142.2 cm (10th centile), and weight was 75th centile. The dysmorphic features were still present. Repeat testing for Fragile X and karyotype revealed similar results. In addition, deletion and duplication at the 22q DiGeorge/VCFS critical region by FISH studies was negative. Skeletal survey was found to be normal. Mutational analysis of MECP2 and SNRPN gene was negative, thus ruling out Rett Syndrome and most forms of Angelman Syndrome.

The patient was seen again in 2012, at the age of 20 years. Interval history revealed worsening of her seizure disorder despite daily medications and newly diagnosed hypertension. She had also developed nocturnal bedwetting, new behavioral problems such as increased aggression, lower threshold arousal, lower adaptability and was enrolled in local adult intervention services. She was found to be overweight with BMI measuring 29.1 (Height: 152.4 cm, Weight: 67 kg). On examination, she continued to be dysmorphic: a round face and prominent forehead, high anterior hairline, prominent blue iris with long eyelashes, right esotropia, long smooth philtrum and thin upper lip, and small anteverted nose (Fig. 1). She was also found to have brachydactyly, short proximally placed thumb, hypoplastic nails and prominent finger pads with hypoplastic distal phalanges (Fig. 1). Results of her cardiac echocardiography and renal ultrasound were found to be within normal limits. The family pedigree is displayed in Fig. 2.
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Fig. 2. The patient’s mother (III-IV) was diagnosed with mild learning disability and scoliosis. The father (III-III) was diagnosed with mild learning disability and apraxia. Patient’s maternal uncle (III-VII) has learning disability and maternal aunt (III-VI) has hypothyroidism. Her maternal grandmother (II-VI) had COPD and hypertension. Paternal grandmother (II-III) had a history of depression, hypertension and migraine. There is also history of Alzheimer’s (I-I), diabetes (I-I) and ADHD (IV-III) on the paternal side of the family.

Materials and Methods

Array comparative genomic hybridization (aCGH) analysis was performed on purified DNA from the proband using a NimbleGen 135K oligonucleotide array (Roche NimbleGen, Madison, WI), and scanned with a DNA Microarray Scanner (Agilent Technologies, Santa Clara, CA). Results were displayed by Genoglyphix v3.0 (Signature Genomic Laboratories, Spokane, WA). Single nucleotide polymorphism (SNP) array analysis was also performed on purified DNA from the proband and mother using an Agilent 180K CGH+SNP oligonucleotide array (Agilent Technologies, Santa Clara, CA). Fluorescence in situ hybridization (FISH) was performed on peripheral blood from the proband, mother, and paternal grandmother using the BAC probe (Invitrogen, Carlsbad, CA) RP11-50E16 (chr7:75,362,579-75,520,758), which is located in the deleted region of 7q11.23-q21.11. FISH analysis and image capture was performed using Isis FISH Imaging System v5.3 software (MetaSystems, Newton, MA). All aCGH, SNP, and FISH procedures were performed according to manufacturer’s protocols.

Results

Microarray analysis performed on purified DNA from the proband revealed a 5.09 Mb deletion (chr7:75,003,647-80,098,598,hg18) located in the 7q11.23-q21.11 region (247 probes) that contained 19 OMIM genes (HIP1, CCL26, CCL24, POR, MDH2, HSPBI, YWHAG, SRCRB4D, ZP3, DTX2, UPK3B, POMZP3, FGL2, PION, PTPNI2, MAGI2, GNAI1, GNAT3, CD36) and 17 non-OMIM genes (RHBDD2, MIR4651, SNORA14A, TMEM120A,
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STYXL1, SRRM3, FDPSL2A, LOC100133091, PMS2P11, LOC100132832, CCDC146, LOC100505854, RSBNIL, TMEM60, PHTF2, RPL13AP17, LOC100505881). The array karyotype for the proband is arr(hg18) 7q11.23q21.11(75,003,647-80,098,559)x1. Array CGH+SNP array analysis was also performed on the proband and mother, and were compared at the deleted 7q11.23-q21.11 region. Informative base-pairs within the deleted region strongly suggest that the maternal allele was deleted in the proband. The father was not available for genetic testing.

FISH analysis was performed on peripheral blood from the proband for deletion confirmation using a BAC probe (RP11-50E16) located in the 7q11.23-q21.11 region. In addition, FISH analysis was performed on peripheral blood from the mother and paternal grandmother to determine carrier status. The deletion was confirmed by FISH analysis in the proband and the FISH karyotype is nuc ish 7q11.23 (RP11-50E16)x1. The mother and paternal grandmother were not found to carry the deletion by FISH analysis.

Discussion

A total of 17 patients, including 16 cases summarized by Marshall et al. (2008) and our patient, had 7q11.23-q21.11 deletions that either spanned or disrupted the MAGI2 gene (Fig. 3). Of these 17 patients, 94.1% (16/17) were reported to have IS or other seizure disorders. Only one patient (5.9%) with a deletion spanning the MAGI2 gene did not have a history of IS or other seizure disorders. In addition, a total of 12 patients were reported by Marshall et al. (2008) to have 7q11.23-q21.1 deletions that did not span the MAGI2 gene. Of these 12 patients, one had a reported history of IS despite the absence of a MAGI2 gene deletion. Röthlisberger et al. (2010) also described a 15-month-old female with documented IS and a 13 Mb deletion (aCGH) encompassing the 7q11.21-q11.23 chromosome region that included the WBSCR, but not the MAGI2 gene (Fig. 3).

Of the genes found within the 7q11.21-q21.11 region, Marshall et al. (2008) and Röthlisberger et al. (2010) both concluded that MAGI2 is the most likely candidate gene for IS, as it encodes for a synaptic scaffolding protein involved in synaptic development.
Thakur, Peffer, Kolthoff, Kochmar, Surti

Seizure Disorder in a Patient with a 5.09 Mb 7q11.23-q21.11 Microdeletion Including the MAGI2 Gene – Peterson, Thakur, Peffer, Kolthoff, Kochmar, Surti

and function (Paciorkowski et al., 2011). Furthermore, animal studies have demonstrated that MAGI2 interacts with many pre- and postsynaptic proteins, including stargazin, a mutated protein causing epilepsy in the stargazer mouse (Deng et al., 2006; Noebels et al., 1990). Indeed, we agree with this hypothesis as 94.1% (16/17) of patients described with 7q11.23-q21.11 deletions that span or disrupt the MAGI2 gene have IS or other seizure disorders. The single patient without seizures may harbor a mutation in an IS-associated gene located outside of the deletion boundaries. The patient described by Röthlisberger et al. (2010) with a 7q21.11 deletion that partially spanned the MAGI2 gene without seizure disorders lacked a clinical history prior to the age of 10.5, thus making it difficult to definitively exclude a history of IS or other seizures.

However, the two patients described by Marshall et al. (2008) and Röthlisberger et al. (2010) with IS and 7q11.21-q11.23 deletions that did not include the MAGI2 gene could be explained by additional genes located within the deletion boundaries. Ramocki et al. (2010) reported on 26 patients from 10 unrelated families with a 7q11.23 deletion located between the WBSCR and the MAGI2 gene that resulted in patients with epilepsy, intellectual disabilities, and neurobehavioral problems. Located within the deleted region is HIP1 (Fig. 3), a candidate gene that is normally expressed in the brain and may contribute to IS or other seizure disorders when deleted or disrupted (Komoike et al., 2010). Indeed, mice knockout models including Hip1± and Hip1−/−, both reported in epilepsy development (Rao et al., 2001 (T. Ross, personal communication with Ramocki)). A total of five patients from Marshall et al. (2008) and the patient reported by Röthlisberger et al. (2010) had deletions spanning the HIP1 gene that did not include the MAGI2 gene, and only 33% (2/6) of these patients had a history of IS. The 7q11.23-q21.11 deletion in our patient also includes the HIP1 gene.

The utilization of high-resolution microarray (aCGH) analysis for defining deletion/duplication boundaries is critical for candidate gene identification. A major limitation of the Marshall et al. (2008) report is the numerous low-resolution breakpoint mapping techniques employed including quantitative real-time PCR (qPCR), fluorescence in-situ hybridization (FISH), microsatellite marker analysis (MMA), and low-resolution arrays. The results of these imprecise mapping techniques are undefined deletion boundaries, some quite large (Fig. 3), that hinder our ability to determine gene involvement. Mapping precise 7q11.21-q21.11 breakpoints (e.g. high-resolution aCGH or sequencing) will be required in the future to resolve the role of candidate genes as they relate to IS and other seizure disorders.

Another possible mechanism for seizure disorders in patients with MAGI2 deletions is based on a recent discovery by Barboux et al. (2012) using high-throughput genotyping arrays that demonstrated polymorphic imprinting of the MAGI2 gene in human placental tissue. As imprinted genes are characterized by monoallelic expression determined by the parent of origin, the deletion of a non-imprinted MAGI2 gene may play a role in abnormal fetal development. However, the mechanism of polymorphic imprinting is currently unknown and will require additional research to determine the significance of this finding.

In conclusion, we report on a 21-year-old female with a history of dysmorphism, seizure disorder, and intellectual disability who was discovered upon aCGH analysis to carry a 5.09 Mb 7q11.23-q21.11 microdeletion that included the MAGI2 gene. FISH analysis confirmed the deletion in the proband, and was not deleted in the mother and paternal grandmother. Although the father was not available for genetic testing, we feel this was a de novo deletion based on the family pedigree (Fig. 2). Based on previously reported 7q11.21-q21.11 deletion cases, and our case, MAGI2 remains the most likely candidate gene for IS and other seizure disorders. However, additional candidate genes including HIP1 may also contribute to seizure disorders independent of MAGI2 deletions. Lastly, the role of polymorphic imprinting as it relates to the MAGI2 gene will be of interest in the future.

Acknowledgements

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References


Case Study

Seizure Disorder in a Patient with a 5.09 Mb 7q11.23-q21.11 Microdeletion Including the MAGI2 Gene – Peterson, Thakur, Peffer, Kolthoff, Kochmar, Surti


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Hyperdiploidy in CLL/SLL: A Rare Cytogenetic Event Associated with Poor Prognosis
Matthew DeNicola, Sheeja Pullarkat, Steven Yea, Nagesh Rao, Lynn Yang, Carlos A. Tirado

Abstract
Hyperdiploidy has been described in a variety of malignancies including acute lymphoblastic leukemia and plasma cell myeloma, in which the abnormality is associated with a very good prognosis. Herein, we describe a 61-year-old female that was diagnosed with atypical chronic lymphocytic leukemia (CLL). Initial chromosome analysis of a lymph node specimen showed an abnormal karyotype described as 46-48,XX,add(3)(q12),+16,+mar[cp3]/46,XX[1]. Chromosome analysis of the bone marrow a week later showed a pseudodiploid and normal diploid clone described as: 46,X,-X,-3,-6,+7,+9,14,-15,+16,+17,+20,-22[1]/46,XX[19]. Concurrent FISH studies of peripheral blood samples using the CLL FISH panel showed nuclei with an extra copy of chromosome 13 and an extra copy of the short arm of chromosome 17. FISH for t(11;14) was negative. These results suggest the presence of an underlying complex hyperdiploid karyotype. Hyperdiploidy is a rare event in SLL/CLL and is usually associated with a poor prognosis.

Introduction
Hyperdiploidy has been described in a variety of malignancies including acute lymphoblastic leukemia and plasma cell myeloma, in which the abnormality is associated with a very good prognosis. Complex karyotypes can be seen in CLL/SLL, and are generally associated with a poor prognosis. Although rare, hyperdiploidy has been observed in CLL/SLL, in which it usually portends a poor prognosis.

Case Presentation
A 61-year-old female presented with an eleven-month history of enlarging lymph nodes in her neck. CT scan revealed bulky confluent lymphadenopathy in the left neck with extension into the superior mediastinum and a large soft tissue density (9.0 x 7.6 cm) overlying the left occipital bone. Her CBC was significant for anemia (Hgb 8.5 gm/dL). SPEP showed two IgM kappa monoclonal proteins. A core biopsy of the left neck mass showed an atypical lymphoid infiltrate that expressed CD5, CD19, CD20, PAX5, BCL2, and IgM and was negative for CD10, CD23, BCL1, BCL6, and IgD. Flow cytometry revealed a monotypic B cell population with kappa light chain restriction and coexpression of CD20 and CD5. Molecular pathology studies were positive for clonal B-cell gene rearrangement. While consideration was given to nodal marginal zone lymphoma, a final diagnosis of atypical small lymphocytic lymphoma (SLL) was made. She received five cycles of bendamustine and rituximab and went on to achieve complete remission by PET-CT.
Methods

Conventional Cytogenetics:

Chromosome analysis was performed using standard cytogenetic techniques on the bone marrow and lymph node of this patient. Twenty metaphase cells were analyzed, and karyotypes were prepared using the Applied Imaging CytoVision software (Applied Imaging, Genetix, Santa Clara, CA). Karyotypes were described according to the ISCN 2013 nomenclature (Shaffer et al., 2013).

FISH

Fluorescence in situ hybridization (FISH) was performed using the CLL Panel: ATM (11q22.3), CEP 12 (centromere 12), D13S319 (13q14.3)/D13S1020 (13q34), TP53 (17p13.1) [5 probes], and IGH (IGH@) dual color, break apart probe (14q32) [2 probes] from Abbott Molecular (Des Plaines, Illinois 60018) on interphase nuclei.

Results

Conventional Cytogenetics

Only four cells were available for analysis on the lymph node due to low mitotic index. Karyotype revealed an abnormal female karyotype with trisomy 16 and a marker chromosome in 3 of 4 cells examined. The analysis also revealed additional material of unknown origin on chromosome 3 with a possible loss of 3q material (Fig. 1). The remaining cell was cytogenetically normal.

Chromosome analysis of the bone marrow one week later revealed a complex, abnormal female karyotype in 1 of 20 cells analyzed, with multiple chromosomal gains (chromosomes 7, 9, 16, 17, and 20) and losses (chromosomes X, 3, 6, 14, 15, and 22) (Fig. 2). These findings corroborate the gain of chromosome 16 and possible loss of chromosome 3q material observed in the initial lymph-node derived karyotype. The clonality of this cell was corroborated by concurrent FISH studies.

FISH

Concurrent FISH analysis of peripheral blood using the CLL panel revealed three copies of chromosome 13 in 13% (39/300) of nuclei examined and three copies of chromosome 17p in 9% (27/300) of nuclei examined. These findings are suggestive of an underlying hyperdiploid karyotype. FISH analysis for t(11;14) was negative.

These findings were described as:

\[
\text{nuc ish(D12Z3x2,D13S319x3,D13S1020x3)} [39/300] \quad \text{(Fig. 3)}
\]

\[
\text{nuc ish(ATMx2,TP53x3)} [27/300] \quad \text{(Fig. 4)}
\]

\[
\text{nuc ish(IGH@x2)} [300].
\]

Discussion

Cytogenetic abnormalities are detected by FISH in up to 80% of cases of CLL/SLL, the most common of which are deletion 13q and trisomy 12. While these changes typically occur as isolated cytogenetic events, complex karyotypes occur in up to 10% of cases of CLL/SLL, and are associated with a poor prognosis (Heim and Mitelman, 2009). Hyperdiploidy is a very rare cytogenetic event
Hyperdiploidy in CLL/SLL: A Rare Cytogenetic Event Associated with Poor Prognosis – DeNicola, Pullarkat, Yea, Rao, Yang, Tirado

in CLL/SLL, and has only been reported in so-called “atypical CLL/SLL,” as in this case, as well as one report in a case of CLL/SLL with increased prolymphocytes (Vundinti et al., 2011). While data is limited, hyperdiploidy in CLL/SLL anecdotally appears to portend a worse prognosis. It is known that CLL/SLL may transform to diffuse large B-cell lymphoma, sometimes associated with trisomy 7 or deletion 14. The current case shows these abnormalities as part of the hyperdiploid karyotype, and not as isolated genetic events. However, it is unclear as to whether hyperdiploid karyotypes that include these abnormalities will progress to large cell lymphoma. A more comprehensive review of cases is needed to determine the outcome of CLL/SLL patients with hyperdiploid karyotypes.

References


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Effects of the Affordable Care Act on our Laboratories

By Jennifer Crawford, CG(ASCP)

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January 2014

Otto von Bismarck, Prussian Statesman and former German Chancellor, once said “laws are like sausages, it is better not to see them being made.” Truth be told, the Affordable Care Act (ACA) is exactly one of those laws. Dating all the way back to the presidency of Theodore Roosevelt in the early 1900s, the United States government has been attempting to work out a suitable medical plan for its growing population. A law was finally passed in 2010. The Patient Protection and Affordable Care Act (PPACA) 2010 HR3590, or Affordable Care Act (ACA) for short, is the new healthcare reform law in America.

The Affordable Care Act is a complex piece of legislation that attempts to reform the healthcare system by providing more Americans with affordable quality health insurance while curbing the growth in healthcare spending. In addition to the more publicized sections dealing with preventive care, insurance coverage, Medicaid and Medicare, provisions in the law help to increase the number of healthcare workers by providing funding for scholarships, promote community health centers, modernize the Indian Health Service (IHS) and promote preventive measures including nutritional information. The ACA does this by not only creating new provisions, but also by amending other laws like the Food, Drug and Cosmetics Act (FD&C) and the Indian Health Service (IHS) and promote preventive measures including nutritional information. The ACA does this by not only creating new provisions, but also by amending other laws like the Food, Drug and Cosmetics Act (FD&C) and the Public Health Services Act.

The implementation of this law spans from 2010 to 2022. A great number of changes can occur over that timespan. One section of ACA dealing with long-term care services, Title VIII, Community Living Assistance Services and Supports Act (CLASS Act), has already been repealed on January 1, 2013. This brings us to today where we’ve seen a messy, bureaucratic battle between parties over implementation of The Affordable Care Act.

The question now for our laboratories is how this new law will affect our business.

As a nation we have already seen changes benefitting our personnel and clients, which include bans on lifetime limits on care, allowing dependents to utilize parents insurance up to the age of 26, and preventive coverage benefits that include free annual wellness visits. These preventive tests include screenings for diabetes and different cancers including breast, cervical and prostate (1). This increase in preventative testing for patients covered under the ACA will lead to an influx of clinical testing for laboratories. As of January 1, 2014, some benefits will prevent providers from discriminating based on pre-existing conditions or the cancellation of policies by provider due to illness, coverage for clinical trials to improve access to innovative medical therapies, and arguably most important, access to quality, affordable healthcare for all Americans who want coverage. The former element has recently faced unforeseen delays in registration due to technical errors with the government website, but once rectified will prove to impact the laboratory most as the accessibility of healthcare coverage to all Americans is expected to increase with new patients somewhere in the range of 30-32 million people by the year 2016 (2).

The question that remains is which of our laboratories will be able to support this increased amount of testing. There is still one policy issue that has yet to be agreed upon from the Centers for Medicare and Medicaid Services (CMS), and that is the Clinical Laboratory Fee Schedule (CLFS)(3). The CLFS sets CMS reimbursement rates for clinical testing, but in its 30 years of existence has done little to keep up with the growing technology and automation of our laboratories. A recent study commissioned by the American Clinical Laboratory Association (ACLA) found that Medicare rates are almost always lower than the average rates paid by private plans (4)(5). What this means for laboratories is that until a rate increase in the CLFS has been agreed upon, it is possible that only those laboratories with the highest volume in testing will be able to compensate financially for this gap in reimbursement from Medicare. More new patients in the coming years mean more testing. It is possible that mainly large, high-volume, commercial or hospital-run laboratories that can successfully negotiate a fiscally beneficial reimbursement plan with Medicare will be the only ones returning a decent monetary benefit from the additional volume.

Along with these factors, there remains one element that we can control when it comes to how this law will impact us both as healthcare consumers and as laboratorians—our initiative to provide feedback to our Congress. The implementation and continued improvement of this law will go on for years and years to come and as a result consumer feedback is of utmost importance. If you are interested in having your voice heard you can visit AGT’s website for further information on writing to your state and local leadership (6).

Sources:

The Journal of the Association of Genetic Technologists 40 (1) 2014
Peter A. Benn, PhD, FACMG, DSc
Interviewed by Dr. Hon Fong L. Mark and Dr. Philip Buchanan

The present profile recognizes Dr. Peter Benn who had been Director of Laboratory Services at the University of Connecticut Health Center in Farmington, Connecticut for many years. Dr. Benn received a PhD from the University of Birmingham, Birmingham, England in 1976. Additional demonstration of expertise successfully led to a DSc from the University of St Andrews, Scotland, in 2006. In addition to cytogenetics, Dr. Benn has extensive experience with prenatal screening for fetal aneuploidy. Professional activities include various duties on behalf of the International Society for Prenatal Diagnosis (ISPD). He married Emily in 1985 and they have two sons, Michael and Steven, now aged 26 and 22, respectively.

HFLM/PB: Where were you and what were you doing in the 1960s (Mark, 2000) and 1970s? What was the field like for you back then?

PAB: When I first went to College in St Andrews, Scotland, in 1967, I actually wanted to be an astronomer. I was amazed, fascinated and absorbed with the beauty of views through a telescope. But that was a path that was neither technically easy nor likely to lead to a career. So, I decided to major in physics. I eventually became interested in radiobiology and the effects of radiation on chromosomes. For me, looking through a microscope was every bit as enjoyable as the telescope. I think I can best describe it as a simultaneous sensory experience of art, scientific curiosity and appreciation of nature. I suspect every cytogeneticist and cytogenetics technologist has the same esthetic experience and that never seems to go away. By the 1970s various new banding methods were being published and it was immensely satisfying when you found they actually worked (Benn and Tantravahi, 2001).

HFLM/PB: What prompted your relocation to America from the United Kingdom?

PAB: My first job was as a research assistant (equivalent to a technologist) in a diagnostic cytogenetics laboratory in Liverpool, England. To really expand my knowledge and pursue a career I needed more education so I entered a PhD program in Birmingham, England. Part of this work involved collaboration with investigators in Philadelphia. Upon completion of my PhD, I moved to Philadelphia, taking a post-doc position.

HFLM/PB: How did you first become interested in prenatal cytogenetic diagnosis?

PAB: Prenatal cytogenetics was an activity that was carried out in the lab where I did my PhD work. Although my PhD project did not involve prenatal diagnosis, I followed the trials and tribulations. The early days of amniotic fluid cell culture were certainly challenging. At that time, those who worked on this considered themselves very fortunate if the cells grew, there was no contamination, and they obtained results. But for all concerned, there was always great satisfaction in either providing reassurance or information that allowed women to make informed choices. Of course, gradually, methods improved and testing became routine. I always had a special fascination with meiotic errors and their consequences. I often say that when we look through the microscope and see meiotic segregation error, we see the consequence of something that occurred at the earliest time of existence. Again, this is not too different from the observational astronomer; looking out to the most distant objects in the cosmos and finding evidence for the creation of the universe.

HFLM/PB: I understand that you are an active researcher as well as a clinician. Please elaborate.

PAB: My research has always been very clinically oriented. This provided a lot of added meaning to the day-to-day provision of clinical diagnostic cytogenetics. I always obtained a lot of satisfaction from interesting cases, interpretation of atypical results, and finding new ways of testing. I would strongly encourage others to become involved in clinical studies, publish interesting cases, and otherwise pursue research endeavors.

HFLM/PB: I heard of your contribution to the field through my role as a Chair of the Cancer Genetics Committee of the New England Regional Genetics Group (NERGG), a Member of the Steering Committee and also a Member of the Prenatal Diagnosis Committee. Please share your experience/elaborate.

PAB: Yes, I too have had my share of committee and support activities and that has provided an opportunity to interact with some very eminent geneticists and other clinicians. But I have to confess that my preference has always been to spend my time on laboratory research activities and especially writing. I have always considered myself fortunate in having excellent supervisory and technical support that has allowed me to focus on the activities that I wanted to pursue.
Dr. Peter A. Benn – Mark and Buchanan

HFLM/PB: Please describe your duties as Associate Director at the Prenatal Diagnosis Lab of New York City.

PAB: In 1988 I moved to New York to be the Associate Director of the Prenatal Diagnosis Laboratory of NYC. Together with Lillian Hsu, the Director, I was able to be involved with numerous studies on mosaicism, maternal cell contamination and other issues in prenatal cytogenetic diagnosis (Benn, 2010). Lillian viewed all of her staff as part of her extended family and leaving that lab to go to a private sector job was a very difficult decision.

HFLM/PB: Best wishes to Dr. Hsu. Please describe your duties as Director of Medical Diagnostics at Lifecodes Corporation at Valhalla, NY.

PAB: Lifecodes was a start-up company that planned to take advantage of developments in molecular genetics as it related to clinical testing, forensics, and paternity testing. They had some very creative and talented scientists, some of whom became well known for their roles in high profile forensic analyses. We did establish a successful cytogenetics and molecular genetics lab. Working in the private sector was a very valuable experience and it was never dull. But I think perhaps I was better suited for an academic environment.

HFLM/PB: In your opinion, what traits better qualify someone in our field for an academic versus a non-academic position?

PAB: For cytogeneticists, the academic world is generally better suited to those who are good teachers, wish to publish, conduct research and success is to a large degree self-determined. In the private sector, the focus is often on expanding the business, increasing productivity, and meeting the overall business objectives. The goals of a company can change rapidly following a merger, new management, etc. The non-academic position is therefore probably better suited to those who prefer a more direct financial-incentive based system, have good marketing and personnel skills, are team players, and can be flexible when presented with change. For technologists, the private sector can be particularly advantageous for those who are highly ambitious and wish to diversify their skills without being inhibited by a highly structured (often unionized) system.

HFLM/PB: Your last move was to Farmington, CT. Please describe.

PAB: One of the major reasons why I decided to work at the University of Connecticut Health Center, Farmington, was the opportunity to establish a maternal serum screening program. In 1988, the triple test was first proposed and I felt sure that this would radically change prenatal diagnosis. Our triple test program at UCONN started in 1991 and it was an immediate success. As new markers in serum and ultrasound emerged (Cuckle and Benn, 2010), we were able to incorporate them. The lab complemented the cytogenetics activities and remained highly innovative up to the time that the program was absorbed into the hospital’s clinical chemistry lab. It always seemed odd to me that more cytogeneticists did not become involved with prenatal screening.

Now, of course, prenatal screening and diagnosis is undergoing major changes as a result of the introduction of cell free fetal DNA (cfDNA) in maternal plasma (Benn et al., 2013). For me, the experience with biochemical and ultrasound markers was invaluable in understanding how the new cfDNA testing should be used.

HFLM/PB: What do you think are the most urgent questions that need to be answered in our field in the coming years?

PAB: I think perhaps the most important set of questions is not really scientific or clinical in scope, it is more social and ethical (Benn and Chapman, 2010). We are rapidly developing a potential capacity to screen and non-invasively diagnose many more conditions including predispositions, late onset disorders and non-medical traits. Which ones should be offered, how do we provide pre-test information, how do we ensure worthwhile tests are available equitably, and how do we prevent discrimination or other damage to individuals and populations?

HFLM/PB: What challenges do you see facing clinical cytogenetics laboratories in the near future? Please discuss the integration of microarrays and next generation sequencing technologies into our labs.

PAB: We are at a remarkable time when molecular genetic technologies are transforming clinical genetics. The integration of microarrays and sequencing is highly complex because it clearly depends on the area of testing (e.g. pediatric, prenatal, cancer, reproductive testing, etc.) as well as the clinical findings in individual cases. Sequencing has already had a huge impact on prenatal testing and it could similarly transform other parts of conventional cytogenetics and microarrays. It is too soon to know, but I suspect we will have an extended period where all three of these technologies are needed. Ultimately the balance will shift more towards those methods that maximize information and reduce overall costs.

HFLM/PB: Do you see genetic testing being performed mainly in large commercial laboratories?

PAB: In the U.S., I think we will see more of the smaller cytogenetics laboratories disappearing. It is extremely difficult for them to compete with the major commercial labs that can invest in the new technologies, offer testing for rare disorders, and contract for global testing with insurance companies. But we do still need to maintain and protect our academic labs so we have training and research for the future. Alliances between academic and private sector labs are likely to become increasingly important.

HFLM/PB: In your opinion, do you think cytogenetics will be dead, as previously predicted? (Please also see discussion in the profile of Dr. David Ledbetter in Mark, 1999.)
Do you see the study of chromosomes being completely replaced?

PAB: I see the field of cytogenetics as being in metamorphosis rather than terminally ill. The concepts of chromosome segregation and rearrangement and their clinical significance are the same regardless of the methods used to identify the karyotype. The interpretation is based on the expertise of cytogeneticists. Arrays and sequencing are transforming technologies in our field but, often happily, we do still need to revert to conventional cytogenetics to fully understand the findings of the molecular methods.

HFLM/PB: This column often ends with a saying or an important piece of advice. Before ending this interview, are there words of wisdom you would like to share with our readers?

PAB: Fresh from the struggle to understand how and when to use microarrays, cytogeneticists and genetics technologists now need to learn about sequencing. It is vital that we do so and not consider this to be outside our area of expertise or a threat to our trade (as I think happened to some extent with prenatal serum screening). Sequencing is, of course, the ultimate genetic technology and perhaps it will remove the largely artificial division that exists between cytogenetics and molecular genetics.

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Reflections on Janet Rowley, MD

By Jennifer Poitras

Editor's Note: The Educator's Profile is departing from its usual format this quarter to reflect on the passing and life of one of the true greats of our profession. On Wednesday, December 17, 2013, Janet Rowley, MD, died of ovarian cancer at the age of 88. While only a few of us in laboratory genetics had the great fortune to know her personally, all of us knew or knew of her professionally.

Although I only knew Dr. Rowley on a professional level, from everything I have heard from those who did know her personally, she was incredibly modest about her own accomplishments. She preferred to focus on the future of our field and the achievements of others, particularly young researchers. It is in that spirit that AGT's tribute to Janet Rowley will not be a long listing of her contributions to the field and awards that she received. Of course, there are things that must be mentioned, but most of this column will be a reflection from one of those young scientists who had the rare good fortune to get to know Dr. Rowley personally.

In 1973 she discovered the chromosomal basis of chronic myeloid leukemia: the translocation between a chromosome 9 and a chromosome 22. By happenstance, that was the year I graduated from college with an undergraduate degree in genetics. That coincidence puts the history of our field into stark perspective for me.

Dr. Rowley's discovery heralded the dawn of cancer cytogenetics which today is the mainstay of most cytogenetics laboratories. Many would also say that it opened the door to the field of genomic and personalized medicine.

In addition to receiving many awards from the scientific community, including the Albert Lasker Clinical Medicine Research Prize in 1998, President Bill Clinton presented Dr. Rowley with the National Medal of Science, also in 1998; in 2009, President Barack Obama bestowed her with the United States' highest civilian honor, the Presidential Medal of Freedom.

Jennifer Poitras is one of those fortunate to have had the opportunity to get to know Janet Rowley on a more personal basis, and she has generously agreed to share her recollections and thoughts about this great woman with JAGT readers.

MBK: Tell me a little about yourself, how you came to meet Janet Rowley, and how she has influenced your life.

JP: I entered the Diagnostic Genetic Sciences Program at the University of Connecticut (UConn) in 2002. Recent scientific milestones, including the completion of the Human Genome Project, and the blockbuster success of Gleevec, had thrust the field of genetics into prominence. I could never have predicted how those two scientific triumphs would, in coordination, facilitate annotation of the cancer genome in the decade to come.

Long before whole genome sequencing, cytogenetics was the basis for global interrogation of the genome. Even in my early years of training, I marveled at how incredible it was that Dr. Rowley's identification and refinement of a single, disease defining chromosomal abnormality had led to development of a curative wonder drug. I also remember hearing that, despite the importance of her discovery, Dr. Rowley had a reputation for exuding humility.

After completing my undergraduate degree at UConn, I worked as a research technician in Dr. Cynthia Morton's lab at Harvard, where the rationale for my project was largely based on Janet Rowley's work. Through cloning the breakpoints of novel chromosomal rearrangements in leukemia patient samples, we hoped to identify new genes associated with leukemogenesis. I found the work fascinating, and in 2009 entered the Human Genetics Predoctoral Training Program at Johns Hopkins University in Baltimore, Maryland, where I am now a PhD candidate and continue to work on the genetic dissection of leukemia.

In retrospect, Dr. Rowley's discoveries influenced my research interests even more than I had realized! As a matriarch and icon in my field of study, Dr. Rowley was a scientist I had dreamed of meeting since my earliest days as a trainee. I feel profoundly fortunate that recently I had the opportunity to spend some time with this extraordinary woman, who inspired me not only to be a better scientist, but more importantly, a better person. It is both an honor and a pleasure to recount what Janet Rowley has meant to me, and that very special time when I got to meet her personally.

The Human Genetics Program at Johns Hopkins is steeped in history and boasts several pioneers in the field of genetic medicine, including the late Barton Childs, MD. Each year, a committee of students in the program selects prominent researchers and invites them to give a lecture at Hopkins in honor of Dr. Childs. In 2011, I served on the selection committee, and insisted that Janet Rowley be included in the list of candidates for the lecture. It turned out that many of my fellow committee members, also recognizing Dr. Rowley's litany of contributions, had listed her as an obvious choice as well. Weeks later, I was elated to learn that the overwhelming majority of our colleagues agreed, and Dr. Rowley was invited to deliver the 2011 Barton Childs Lecture.

When she arrived in Baltimore I made it my mission to spend as much time with Dr. Rowley as possible. I wanted
to glean every ounce of wisdom she had to offer. Suddenly, the woman I’d been longing to meet for a decade was standing before me in a lavender tweed suit with a cheerful, welcoming, and entirely unassuming disposition. Through candid discussions about family, the field, and women in science, I came to know the Janet Rowley that was so highly esteemed by my mentors.

I picked her up in the morning to take her to meet Dr. Bert Vogelstein, and was immediately struck with her sustained passion for science. On the way to Bert’s office, we discussed current topics in cancer genetics, including imbalances surrounding the t(9;22) breakpoint, and conflicting correlations with patient outcome. Beyond the scientific conversation, her genuine excitement to see Bert, as both a friend and fellow scientist, is something I will never forget. This collegial attitude echoed innumerable times throughout her visit.

Despite her numerous accolades and achievements, Dr. Rowley was perhaps the most humble person I have ever met. With remarkable grace and humility, she repeatedly minimized the importance of her own work, while acknowledging and highlighting the efforts of others. She opened her lecture by stating, “I’m not going to speak much about my own work because you already know that story. Instead, I’m going to focus on recent advancements and the future of the field.” Throughout the day, she reiterated, “Let’s face it. Looking at chromosomes isn’t rocket science. If I didn’t figure it out, someone else would have.” It was refreshing to meet a legendary scientist who viewed science as a collaborative community, respecting every investigator’s contributions as part of a larger endeavor.

At dinner I had the opportunity to ask Dr. Rowley to comment on the future utility of cytogenetics, given the burgeoning integration of sequencing and high resolution genomic analyses in the clinic. She told me that cytogenetics would not disappear, but that a structural overhaul was imminent, merging molecular and cytogenetics laboratories. To that end, such a union would require the ability of both disciplines to adapt and work together, to deliver the most accurate and efficient patient care.

While Janet Rowley’s landmark discoveries redefined the paradigm for cancer genetics and therapeutics, the most important lessons I learned from her visit were more personal in nature. Her inherent modesty and unrelenting fervor represent the character of a truly distinguished scientist, whose goal was simply to advance the field with little interest in personal recognition. As academic research steadfastly marches forward, I hope we can proceed following Dr. Rowley’s example, remembering that successful scientific discovery is truly a team effort. Similarly, as diagnostic laboratories navigate the complicated road ahead, my hope is that molecular genetics and cytogenetics will unite in the spirit of Janet Rowley, recognizing the important contributions that each discipline makes toward creating a complete and accurate diagnostic profile.

MBK: Thank you, Jen, for sharing your personal reminiscences of this great woman. Though most of us never had the opportunity you did, Dr. Rowley was a friend to all in our profession, from trainees to technologists, to laboratory directors and researchers, and clinicians, and we will all miss her. She was one of the greats.

Footnote: Janet Rowley spoke at the 36th Annual Meeting of the Association of Genetic Technologists (AGT) in Minneapolis, Minnesota in 2011. The PowerPoint slides from her session are posted on the AGT website http://www.agt-info.org in the Members Only section. Additionally, a short interview with Dr. Rowley, conducted at that meeting by Marilyn Arsham, can be viewed on the AGT website.
Brain Tickler Summary

(continued)
Brain Tickler Summary
(continued)

Results: 46,X,der(X)t(X;Y)(q13;p11.2)(20)

In all cells there was a normal X chromosome and a derivative X with most of the long arm missing and what appeared to be Y long arm material attached. FISH for SRY on Yp11.3 was negative, and the normal and derivative X chromosomes contained alpha satellite X material. The presence of Yq was confirmed using a probe for DYZ1, showing signal for Yq12 heterochromatic material. 200 interphase cells exhibited two normal signal patterns for the X centromere. The presence of Y chromosome material in females increases risk for gonadoblastoma. Genetic counseling was recommended.
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Test Yourself #1, 2014

Readers of The Journal of the Association of Genetic Technologists are invited to participate in this “open book test” as an opportunity to earn Contact Hours. AGT offers 3 Contact Hours for this Test Yourself based on articles in Volume 39, Number 4, Fourth Quarter 2014 of the Journal.

Test Yourself is free to AGT members and $30 for non-members. To take this exam, send a copy of your completed Answer Sheet along with the completed CEU Reporting Form to the AGT Education Committee Representative in your region. The list of representatives is on page 38 of this issue. Non-members should submit a check payable to AGT for $30 with their answer sheet. Entry material must be post-marked on or before June 1, 2014.


1. The ENCODE project:
   I. maps regions of transcription
   II. integrates results from various experiments
   III. has provided insight into regulation of genes
   IV. has used 164 different cell lines
   a. I, II and IV
   b. II, III and IV
   c. I, II and III
   d. All of the above

2. All of the following are true, except:
   a. Humans are born microbially sterile
   b. The Human Microbiome Project involves many laboratories in the US
   c. There is a large microbial variation among individuals
   d. There is more variability between any two individuals in terms of their microbes than in their DNA

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Association of Genetic Technologists

CEU REPORTING FORM

Name: [Insert Name]

Address: [Insert Address]

City State Zip Code

Country: [Insert Country]

Email Address: [Insert Email Address]

Program Title/Activity: Test Yourself, 1st Quarter 2014

Date(s) of Publications: 1Q 2013, 2Q 2014

CEU Area (1, 2, 3, 4): →

CEUs Awarded/Requested: 0.3

AGT Membership Number:

Institution, Association, Journal, etc.

Sponsor Organization: P.O. Box 19193

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I hereby certify that I have completed the requirements for the continuing education activity requested above. Please attach appropriate documentation to support this CEU request.

Signature (member) Date Education Committee Approval Date

2/14

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3. Vanderbilt University has created a biobank of DNA samples from 164,000 patients, whose phenotypes are publicly posted.
   a. True
   b. False

4. The Cancer Genome Atlas is an international effort led by:
   a. the Alberts panel.
   b. NCATS at the NIH.
   c. NIH/NHGRI.
   d. University of Chicago.

5. The National Museum of Natural History in Washington, DC:
   I. developed a new exhibit in collaboration with NHGRI: “Genome: Unlocking Life’s Code.”
   II. has a collection of about 400,000 plant species.
   III. is working to create the “Encyclopedia of Life” website.
   IV. has research stations all over the world.
   a. I, II and III
   b. I, II and IV
   c. I, III and IV
   d. II, III and IV

The following questions are from Ivanov A et al. MLL Rearrangement and EVI1 Deletion in BCR/ABL1 Positive Chronic Myeloid Leukemia. J Assoc Technol. 2013;39(4):190-194.

6. The ELL gene on chromosome 19q13.1 encodes an RNA polymerase elongation factor that activates the elongation by suppressing transient passing along the DNA.
   a. True
   b. False

7. Additional chromosomal abnormalities in Ph-positive cells are:
   a. seen in 90% in blast crisis.
   b. mostly +8, +der (22) t(9;22), i(17q) and +21.
   c. seen in 5% cases at diagnosis.
   d. only +8 and +der(22) t(9;22).

8. All of the following are true, except:
   a. Chronic Myeloid Leukemia arises as a consequence of a reciprocal translocation between chromosomes 9 and 22
   b. In CML, additional chromosomal abnormalities are non-random and include trisomy 9 and iso 17q
   c. The MLL gene is located on 11q23 and is frequently rearranged in AML and ALL
   d. The course of CML is characteristically triphasic

9. t(11;19)(q23;p13.1):
   a. is typically seen in de novo and therapy related ALL.
   b. The FAB types of AML patients with t(11;19) as a sole abnormality are M4 and M6.
   c. seems to correlate with a monocytoid differentiation.
   d. has been previously reported in three other CML cases in combination with t(9;22).


10. B-lymphoblastic leukemia/lymphoma:
   a. accounts for about 60% of childhood acute lymphoblastic leukemia.
   b. has a peak incidence between two and five years of age.
   c. is a neoplasm of mature B cells.
   d. represents a major pediatric cancer in under developed countries.

11. The t(11;19)(q23;p13.3) is considered a hallmark of the pre-B ALL phenotype.
   a. True
   b. False

12. All of the following are true except:
   a. Rearrangements of the MLL gene at 11q23 in pediatric ALL is considered an adverse prognostic factor.
   b. B-lymphoblastic leukemias with MLL gene rearrangements are the most common leukemias in infants <1 year of age.
   c. The most common partner in translocations with the MLL gene in B-ALL is the AF4 gene on chromosome 6q21.
   d. The t(4;11)(q12;q23) deregulates the MLL gene, therefore targeting leukomogenesis.


13. Which of the following are the responsibilities of the Quality Assurance program?
   I. Identify and correct problems
   II. Assure the adequacy and competency of staff
   III. Oversee the validation and optimization of new assays in the lab
   IV. Accurate, reliable and prompt reporting of test results
   a. I and II
   b. I, II and III
   c. I, III, and IV
   d. I, II, and IV

14. In observance of the old mantra, “If it is not written down, it did not happen,” the lab is always responsible for initiating corrective action and documenting all its activities of quality assurance when and if the event problems do arise.
   a. True
   b. False
15. What method implemented by CMS will replace the equivalent quality control (EQC) method by introducing more flexibility and customization of quality control policies?
   a. CLIA 2003 final rule (Sect. 493.1256)
   b. IVD manufacturer recommended QC procedures
   c. Individualized Quality Control Plan (IQCP)
   d. None of the above.

16. Advantages of this new plan to traditional QC as defined by CLIA regulations are all the following except:
   a. customization of each test in its own environment with use of electronic and integrated controls.
   b. changes nonequivalent to the CLIA regulatory policies published in 2003.
   c. flexibility in achieving quality control compliance through the use of current technology.
   d. All of the above.

The following are questions from an interview by Dr. Hon Fong L. Mark and Dr. Frank Grass of John E. Wiley, PhD, FACMG in Profiles and Perspectives, J Assoc Genet Technol. 2013;39(4):199-201.

17. Where did Dr. Wiley complete his PhD degree in 1981?
   a. East Carolina University
   b. University of Wisconsin in Madison
   c. University of North Carolina in Greensboro
   d. Boston University

18. What course in his undergraduate career helped Dr. Wiley see the "great potential of genetics in basic research and clinical applications" in 1972?
   a. Karyotyping
   b. Neurospora crassa genetics
   c. Cytogenetics and Amphibian systematics
   d. Embryology

19. According to Dr. Wiley, what are the most urgent scientific questions that need to be answered in our field in the coming years?
   a. Clinical consequences of CNVs detected by microarray and incidental findings from sequencing
   b. Determination of the role of epigenetics in the development of genetic conditions
   c. Identifying the factors that play in multifactorial genetic diseases
   d. All of the above.

20. What challenge does Dr. Wiley identify as the most daunting for clinical cytogenetic laboratories to face in the near future?
   a. Replacing FISH with microarray platforms
   b. Utilizing microarray beyond constitutional analysis testing for prenatal diagnosis, products of conception, and cancer
   c. Proper and adequate reimbursement for the most current diagnostic technologies
   d. Integration of Next Generation Sequencing pipelines


21. What is Mr. Gasparini's current position?
   a. Chief Scientific Officer of NeoGenomics Laboratories
   b. Assistant Director of the Cytogenetics Laboratory at Baystate Medical Center
   c. Assistant Director of Cytogenetics Laboratory of the Prenatal Diagnosis Center
   d. Director of Genetics Division of US Laboratories.

22. How did Mr. Gasparini first enter the field of cytogenetics?
   a. Part-time student and full-time cytogenetic technologist for a pediatric geneticist
   b. Volunteer in a cytogenetics lab at UConn Medical Center
   c. Dropped out of UConn's Liberal Arts program in pursuit of a biology degree
   d. None of the above

23. Whom does Mr. Gasparini consider a mentor in cancer genetics?
   a. Dr. Robert Greenstein
   b. Dr. Solveig Fleuger
   c. Dr. Wayne Miller
   d. Dr. Gordon Dewald

24. What were some personal accomplishments cited by Mr. Gasparini as his career highlights?
   a. Starting the UConn cytogenetics education program
   b. Recipient of the AGT Technologist of the Year lifetime achievement award
   c. Both A and B.
   d. Neither A nor B.
2013-2014 AGT Education Committee Regional Representatives

If you have questions or experience difficulty locating your representative, please contact the AGT Education Director (see page 53 for address).

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Continuing Education Opportunities
AGT Journal Clubs

Journal Clubs are a great way to earn Contact Hours without leaving your home or lab! Journal Clubs can be completed as a group or individually. Each Journal Club includes a reading list, several discussion questions and a post-test. The discussion questions provide a starting point for group discussion, and give individuals taking a Journal Club questions to consider while reading the articles. The post-test is taken after reading the articles and are returned to the regional representatives of the Education Committee to be graded.

Each successfully completed Journal Club is worth 4 Contact Hours. The new Journal Clubs, as well as Journal Clubs #37-#114, can be ordered through the AGT Executive Offices.

READING LIST 37 – General Content Area: Pharmacogenetics and Pharmacogenomics – 2002
1. Pharmacogenetics
2. Consent and Privacy in Pharmacogenetic Testing
4. Mapping a Role for SNPs in Drug Development

READING LIST 38 – General Content Area: Hematologic Malignancies – 2002
1. Double Minute Chromosomes in Acute Myeloid Leukemia and Myelodysplastic Syndrome: Identification of New Amplification Regions by Fluorescence In Situ Hybridization and Spectral Karyotyping
2. Common Fragile Sites Associated with the Breakpoints of Chromosomal Aberrations in Hematologic Neoplasms
3. High Frequency of Leukemic Clones in Newborn Screening Blood Samples of Children with B-precursor Acute Lymphoblastic Leukemia

READING LIST 39 – General Content Area: Molecular Topics: Solid Tumors – 2002
1. Prediction by FISH Analysis of the Occurrence of Wilms Tumor in Aniridia Patients
2. Comprehensive Karyotyping of the HT-29 Colon Adenocarcinoma Cell Line
3. Cytogenetic Clues to Breast Carcinogenesis

READING LIST 40 – General Content Area: Molecular Topics – 2002
1. From Chromosomal Alterations to Target Genes for Therapy: Integrating Cytogenetics and Functional Genomic Views of the Breast Cancer Genome
2. High-throughput Genomic and Proteomic Analysis Using Microarray Technology
3. DNA Analysis in a Paternity Case Involving a Triploid Fetus

READING LIST 41 – General Content Area: Chromosomal Abnormalities – 2002
1. Identification of Uniparental Disomy in Phenotypically Abnormal Carriers of Isochromosomes or Robertsonian Translocations
2. Chromosome 13q Neocentromeres: Molecular Cytogenetic Characterization of Three Additional Cases and Clinical Spectrum

READING LIST 42 – General Content Area: Genetic Counseling – 2003
1. Categorizing Genetic Tests to Identify Their Ethical, Legal, and Social Implications
2. Genetic Counseling for Sex Chromosome Abnormalities
3. Carrier Testing in Fragile X Syndrome: When to Tell and Test

READING LIST 43 – General Content Area: Review Articles – 2003
1. Cancer Genetics
2. Nature Reviews: Genetics
3. Neocentromeres: Role in Human Disease, Evolution, and Centromere Study

READING LIST 44 – General Content Area: Chromosome Positioning – 2003
1. Chromosome positioning in the interphase nucleus
2. Evolutionary conservation of chromosome territory arrangements in cell nuclei from higher primates
3. Non-random radial arrangements of interphase chromosome territories: evolutionary considerations and functional implications

READING LIST 45 – General Content Area: Treatment-Related Hematologic Disorders – 2003
1. 11q23 balanced chromosome aberrations in treatment-related myelodysplastic syndromes and acute leukemia: report from an international workshop
2. 21q22 balanced chromosome aberrations in therapy-related hematologic disorders: report from an international workshop
3. Balanced chromosome abnormalities inv(16) and t(15;17) in therapy-related myelodysplastic syndromes and acute leukemia: report from an international workshop

READING LIST 46 – General Content Area: Mitochondrial Disorders – 2003
1. The genetics and pathology of oxidative phosphorylation
2. Detection of mitochondrial DNA mutations by temporal temperature gradient gel electrophoresis
3. Comprehensive scanning of the entire mitochondrial genome for mutations

READING LIST 47 – General Content Area: Prenatal Testing – 2003
1. Prenatal Diagnosis of Down Syndrome: Ten Year Experience in the Israeli Population

READING LIST 48 – General Content Area: Hematologic Malignancies – 2004
1. Molecular Cytogenetic Aspects of Hematological Malignancies: Clinical Implications

READING LIST 49 – General Content Area: Miscellaneous Topics – 2004
1. The Burden of Genetic Disease on Inpatient Care in a Children’s Hospital
2. Contribution of Malformations and Genetic Disorders to Mortality in a Children’s Hospital
3. A Study of Reciprocal Translocations and Inversions Detected by Light Microscopy With Special Reference to Origin, Segregation, and Recurrent Abnormalities

READING LIST 50 – General Content Area: Cancer Genetics – 2005
1. Cytogenetics and Molecular Genetics of Lung Cancer
2. Chromosome Abnormalities May Correlate With Prognosis in Burkitt/Burkitt-Like Lymphomas of Children and Adolescents: A Report from Children’s Cancer Group Study CCG-E08
3. Clinical Applications of BCR-ABL Molecular Testing in Acute Leukemia

READING LIST 51 – General Content Area: Cancer Genetics – 2005
1. Cytogenetic Profile of Myelodysplastic Syndromes with Complex Karyotypes: An Analysis Using Spectral Karyotyping
2. Classical Hodgkin Lymphoma is Associated with Frequent Gains of 17q
3. Specific Chromosome Aberrations in Peripheral Blood Lymphocytes are Associated with Risk of Bladder Cancer

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Continuing Education Opportunities

READING LIST 52 – General Content Area:
New Technologies – 2005
2. A New Chromosome Banding Technique, Spectral Color Banding (SCAN), for Full Characterization of Chromosomal Abnormalities
3. Molecular Cytogenetic Analysis of Complex Chromosomal Rearrangements in Patients with Mental Retardation and Congenital Malformations: Delineation of 7q21.11 Breakpoints
4. Use of Targeted Array-Based CGH for the Clinical Diagnosis of Chromosomal Imbalances: Is Less More?

READING LIST 53 – General Content Area:
Genetic Syndromes – 2005
1. Five Years of Molecular Diagnosis of Fragile X Syndrome (1997-2002): A Collaborative Study Reporting 95% of the Activity in France
2. Changing Demographics of Advanced Maternal Age (AMA) and the Impact on the predicted incidence of Down Syndrome in the United States: Implications for Prenatal Screening and Genetic Counseling
3. “Everybody in the World is My Friend” Hypersociability in Young Children with Williams Syndrome

READING LIST 54 – General Content Area:
Chromosome Breakage Syndromes – 2006
1. Chromosome Breakage Syndromes and Cancer
2. DEB Test for Fanconi Anemia Detection in Patients with Atypical Phenotype

READING LIST 55 – General Content Area:
Array-based Prenatal Genetics – 2006
1. Array-based Comparative Genomic Hybridization Facilitates Identification of Breakpoints of a Novel der(1)(q11.2; 18)(p36.3; q23) in a Child Presenting with Mental Retardation
2. Detection of Cryptic Chromosome Aberrations in a Patient with a Balanced t(1; 9)(p34.2; p26) by Array-based Comparative Genomic Hybridization
3. Jumping Translocations in Multiple Myeloma

READING LIST 56 – General Content Area:
Leukemia – 2007
1. Fluorescence in situ Hybridization Analysis of Minimal Residual Disease and the relevance of the der(9) Deletion in imatinib-treated Patients with Chronic Myeloid Leukemia
2. Characterization of the t(17; 19) Translocation by Gene-specific Fluorescent in situ Hybridization-based Cytogenetics and Detection of the E2A-HLF Fusion Transcript and Protein in Patient’s Cells
3. Combination of Broad Molecular Screening and Cytogenetic Analysis for Genetic Risk Assignment and Diagnosis in Patients with Acute Leukemia

READING LIST 57 – General Content Area:
Premature Chromosome Condensation – 2007
1. Premature Chromosome Condensation in Humans Associated with Microcephaly and Mental Retardation: A Novel Autosomal Recessive Condition
2. Chromosome Condensation: DNA Compaction in Real Time
3. Phosphatase inhibitors and Premature Chromosome Condensation in Human Peripheral Lymphocytes at Different Cell-Cycle Phases

READING LIST 58 – General Content Area:
Solid Tumor and FISH – 2007
1. Methylthioadenosine Phosphorylase Gene Deletions are Frequently Detected by Fluorescence in situ Hybridization in Conventional Chondrosarcoma
2. Solid Pseudopapillary Neoplasms of the Pancreas are Associated with FLI-1 Expression, but Not with EWS/FLI-1 Translocation
3. High Incidence of Chromosome 1 Abnormalities in a Series of 27 Renal Oncocytomas: Cytogenetic and Fluorescent In Situ Hybridization Studies

READING LIST 59 – General Content Area:
Accounting for the Development of c-MET Mutation
1. Distribution of Insulin-Treated Patients with or without Growth Hormone Treatment
2. Cause of Sudden, Unexpected Death of Prader-Willi Syndrome Patients with or without Growth Hormone Treatment

READING LIST 60 – General Content Area:
Genetics of Autism
1. 15q11-13 GABAAa Receptor Genes are Normally Bi-allelically Expressed in Brain yet are Subject to Epigenetic Dysregulation in Autism-Spectrum Disorders
2. Characterization of an Autism-Associated Segmental Maternal Heterodisomy of the Chromosome 15q11-13 Region
3. 15q Duplication Associated with Autism in a Multiplex Family with a Familial Cryptic Translocation t(14; 15)(q11.2; q13.3) Detected Using Array-CGH

READING LIST 61 – General Content Area:
Genetics of Nicotine Addiction
1. Fine Mapping of a Linkage Region on Chromosome 7p13 Reveals that GABARAP and DLG4 are Associated with Vulnerability to Nicotine Dependence in European-Americans
2. Genomewide Linkage Scan for Nicotine Dependence: Identification of a Chromosome 5 Risk Locus
3. Genetic Linkage To Chromosome 22q12 for a Heavy-Smoking Quantitative Trait in Two Independent Samples

READING LIST 62 – General Content Area:
Somatic Mutation Detection
1. Interfering Somatic Mutation Rates Using the Stop-Enhanced Green Fluorescent Protein Mouse
2. Paternal Age at Birth is an Important Determinant of Offspring Telomere Length
3. Genome-Wide SNP Assay Reveals Structural Genomic Variation, Extended Homozygosity and Cell-line Induced Alterations in Normal Individuals

READING LIST 63 – General Content Area:
Polyglutamine Neurodegenerative Disorders
1. CAG-Encoded Polyglutamine Length Polymorphism in the Human Genome
2. Polyglutamine Neurodegenerative Diseases and Regulation of Transcription: Assembling the Puzzle
3. Pathogenesis and Molecular Targeted Therapy of Spinal and Bulbar Muscular Atrophy

READING LIST 64 – General Content Area:
Clinical Applications of Noninvasive Diagnostic Testing
1. Digital PCR for the Molecular Detection of Fetal Chromosomal Aneuploidy
2. Noninvasive Testing for Colorectal Cancer: A Review
3. Novel Blood Biomarkers of Human Urinary Bladder Cancer

READING LIST 65 – General Content Area:
Diabetes
1. The Development of c-MET Mutation Detection Assay
2. Molecular Mechanisms of Insulin Resistance in Chronic Hepatitis C
3. A Genetic Diagnosis of HNF1A Diabetes Alters Treatment and Improves Glycaemic Control in the Majority of Insulin-treated Patients

READING LIST 66 – General Content Area:
Role of Human Papillomavirus and Associate Biomarkers in Cervical Cancer
1. Distribution of Human Papillomavirus Genotypes in Invasive Squamous Carcinoma of the Vulva
2. Distribution of HPV Genotypes in 282 Women with Cervical Lesions: Evidence for Three Categories of Intraepithelial Lesions Based on Morphology and HPV Type
3. Evaluation of Linear Array Human Papillomavirus Genotyping Using Automatic Optical Imaging Software
Continuing Education Opportunities

READING LIST 67 – General Content Area: Pancreatic Cancer and Its Biomarkers
1. Molecular Profiling of Pancreatic Adenocarcinoma and Chronic Pancreatitis Identifies Multiple Genes Differentially Regulated in Pancreatic Cancer
2. Effect of Recombinant Adenovirus Vector Mediated Human Interleukin-24 Gene Transfection on Pancreatic Carcinoma Growth
3. Highly Expressed Genes in Pancreatic Ductal Adenocarcinomas: A Comprehensive Characterization and Comparison of the Transcription Profiles Obtained from Three Major Technologies

READING LIST 68 – General Content Area: Influenza A(H1N1) Virus
1. Detection of Influenza A(H1N1)Virus by Real-Time RT-PCR
2. Economic Consequences to Society of Pandemic H1N1 Influenza 2009 – Preliminary Results for Sweden
3. Response after One Dose of a Monovalent Influenza A (H1N1) 2009 Vaccine — Preliminary Report

READING LIST 69 – General Content Area: The Development of c-MET Mutation Detection Assay
1. Somatic Mutations in the Tyrosine Kinase Domain of the MET Proto-Oncogene in Papillary Renal Carcinomas
2. Expression and Mutational Analysis of MET in Human Solid Cancers
3. Role of cMET Expression in Non-Small-Cell Lung Cancer Patients Treated with EGFR Tyrosine Kinase Inhibitors

READING LIST 70 – General Content Area: Molecular Cardiology
1. Identification of a Pleiotropic Locus on Chromosome 7q for a Composite Left Ventricular Wall Thickness Factor and Body Mass Index: The HyperGEN Study
3. Genome-Wide Association Study Identifies Single-Nucleotide Polymorphism in KCNB1 Associated with Left Ventricular Mass in Humans: The HyperGEN Study

READING LIST 71 – General Content Area: Detection of Clarithromycin Resistance in Helicobacter pylori
1. Rapid Detection of Clarithromycin Resistance in Helicobacter pylori Using a PCR-based Denaturing HPLC Assay
2. Rapid Screening of Clarithromycin Resistance in Helicobacter pylori by Pyrosequencing
3. Quadruplex Real-Time PCR Assay Using Allele-Specific Scorpion Primers for Detection of Mutations Conferring Clarithromycin Resistance to Helicobacter pylori
4. Rapid Detection of Clarithromycin Resistance
5. High-Resolution Genomic Profiles Define Distinct Clinico-pathogenetic Subgroups of Multiple Myeloma Patients

READING LIST 72 – General Content Area: Werner Syndrome Gene
1. Telomeric protein TRF2 protects Holliday junctions with telomeric arms from displacement by the Werner syndrome helicase
2. WRN controls formation of extrachromosomal telomeric circles and is required for TRF2DeltaB-mediated telomere shortening
3. Sequence-specific processing of telomeric 3’ overhangs by the Werner syndrome protein exonuclease activity

READING LIST 73 – General Content Area: Diagnosis of Melanoma Using Fluorescence in Situ Hybridization
1. Using Fluorescence in situ Hybridization (FISH) as an Ancillary Diagnostic Tool in the Diagnosis of Melanocytic Neoplasms
2. Transcriptomic versus Chromosomal Prognostic Markers and Clinical Outcome in Uveal Melanoma
3. Detection of Copy Number Alterations in Metastatic Melanoma by a DNA Fluorescence In situ Hybridization Probe Panel and Array Comparative Genomic Hybridization: A Southwest Oncology Group Study (S9431)

READING LIST 74 – General Content Area: Role of Short Interfering RNA in Gene Silencing
1. Highly Specific Gene Silencing by Artificial miRNAs in Rice.
2. Gene silencing by RNAi in mouse Sertoli cells.
3. Retrovirus-delivered siRNA.

READING LIST 75 – General Content Area: Multiple Myeloma: Molecular Markers and Tests
1. Multiple Myeloma: Lusting for NF-κB
2. Functional Interaction of Plasmacytoid Dendritic Cells with Multiple Myeloma Cells: A Therapeutic Target
3. High-resolution genomic profiles define distinct clinico-pathogenetic subgroups of multiple myeloma patients

READING LIST 76 – General Content Area: Colorectal Cancer and Loss of Imprinting of IGF2
1. Loss of imprinting of IGF2 as an epigenetic marker for the risk of human cancer
2. Temporal stability and age-related prevalence of loss of imprinting of the insulin-like growth factor-2 gene
3. Epigenetics at the Epicenter of Modern Medicine.

READING LIST 77 – General Content Area: Health Effects Associated with Disruption of Circadian Rhythms
1. Circadian Polymorphisms associated with Affective Disorders
2. A new approach to understanding the impact of Circadian Disruption on Human Health
3. Circadian Rhythm and its Role in Malignancy

READING LIST 78 – General Content Area: Role of Hedgehog Signaling Pathway in Diffuse Large B-Cell Lymphoma
1. Sonic hedgehog signaling proteins and ATP-binder case 62 are aberrantly expressed in diffuse large B-cell lymphoma
2. Sonic Hedgehog Signaling Pathway is Activated in ALK-Positive Anaplastic Large Cell Lymphoma
3. Sonic Hedgegog is Produced by Follicular Dendritic Cells and Protects Germinal Center B Cells from Apoptosis

READING LIST 79 – General Content Area: Whole Genome Amplification & 1986 Chernobyl, Ukraine Nuclear Power Plant Accident
1. BAC-FISH assays delineate complex chromosomal rearrangements in a case of post-Chernobyl childhood thyroid cancer.
2. Whole Genome Amplification Technologies – Eliminating the Concern Over Running Out of DNA Samples Mid Experiment.
3. A break-apart fluorescence in situ hybridization assay for detecting RET translocation in papillary thyroid carcinoma.

READING LIST 80 – General Content Area: Expression of miRNA in Diffuse Large B-Cell Lymphoma
1. Differentiation stage specific expression of miRNAs in B lymphocytes and diffuse large B-cell lymphomas.
2. Coordinated Expression of MicroRNA-155 and Predicted Target Genes in Diffuse Large B-cell Lymphoma.
3. Specific expression of miR-17-5p and miR-127 in testicular and central nervous system diffuse large B-cell lymphoma.

READING LIST 81 – General Content Area: The Genetics of Bipolar Disorder
1. Gene-wide analyses of genome-wide association data sets: evidence for multiple common risk alleles for schizophrenia and bipolar disorder and for overlap in genetic risk
2. Subcortical Gray Matter Volume Abnormalities in Healthy Bipolar Offspring: Potential Neuroanatomical Risk Marker for Bipolar Disorder?
3. Genetic and Environmental Influences on Pro-inflammatory Monocytes in Bipolar Disorder

READING LIST 82 – General Content Area: Role and Detection of Human Endogenous Retroviruses in Rheumatoid Arthritis
1. Increase in Human Endogenous Retroviruses ERV/K-HML-2 Viral Load in Active Rheumatoid Arthritis.
2. A role for human endogenous retrovirus-K (HML-2) in rheumatoid arthritis: investigating mechanisms of pathogenesis
3. Lack of Detection of Human Retrovirus-5 Proviral DNA in Synovial Tissue and Blood Specimens From Individuals With Rheumatoid Arthritis or Osteoarthritis.

The Journal of the Association of Genetic Technologists 40 (1) 2014
Continuing Education Opportunities

READING LIST 83 – General Content Area: Roles of Oncogenes in Breast Cancer
2. Dysregulated miR-183 inhibits migration in breast cancer cells.

READING LIST 84 – General Content Area: Elevated Levels of Human Endogenous Retrovirus-W in Patients With First Episode of Schizophrenia
2. Endogenous Retrovirus Type W GAG and Envelope Protein Antigenemia in Serum of Schizophrenic Patients.
3. Reduced Expression of Human Endogenous Retrovirus (HERV)-W GAG Protein in the Cingulate Gyrus and Hippocampus in Schizophrenia, Bipolar Disorder, and Depression.

READING LIST 85 – General Content Area: Esophageal Cancer
1. The Changing Face of Esophageal Cancer
2. Epidermal Growth Factor-Induced Esophageal Cancer Cell Proliferation Requires Transactivation of β-Adrenoreceptors
3. Esophageal cancer risk by type of alcohol drinking and smoking: a case-control study in Spain

READING LIST 86 – General Content Area: p53 Family and Its Role in Cancer

READING LIST 87 – General Content Area: Proteins Involved with Chronic Myeloid Leukemia and Other Myeloproliferative Disorders
1. Gain-of-Function Mutation of JAK2 in Myeloproliferative Disorders.
2. Kinase domain mutants of Bcr enhance Bcr-Ab1 oncogenic effects.
3. Destabilization of Bcr-Ab1/Jak2 Network by a Jak2/Ab1 Kinase Inhibitor ON044580 Overcomes Drug Resistance in Blast Crisis Chronic Myelogenous Leukemia (CML).

READING LIST 88 – General Content Area: DNA Topology
1. The why and how of DNA unlinking.
2. Bacterial DNA topology and infectious disease.
3. DNA topoisomerase II and its growing repertoire of biological functions.

READING LIST 89 – General Content Area: Waldenstrom Macroglobulinemia
1. Spontaneous splenic rupture in Waldenstrom’s macroglobulinemia.
2. How I Treat Waldenstrom’s Macroglobulinemia.
3. International prognostic scoring system for Waldenström Macroglobulinemia.

READING LIST 90 – General Content Area: Next Generation Sequencing Platforms
1. Rapid whole-genome mutational profiling using next-generation sequencing technologies.
3. Evaluation of next generation sequencing platforms for population targeted sequencing studies.

READING LIST 91 – General Content Area: Hutchinson-Gilford Progeria Syndrome
1. Epidermal expression of the truncated prelamina causing Hutchinson-Gilford progeria syndrome: effects on keratinocytes, hair and skin.
2. Defective Lamin A-Rb Signaling in Hutchinson-Gilford Progeria Syndrome and Reversal by Farnesyltransferase Inhibition
3. Increased expression of the Hutchinson-Gilford progeria syndrome truncated lamin a transcript during cell aging.

READING LIST 92 – General Content Area: Severe Combined Immunodeficiency Screening and Patient Studies
1. Long-term Outcome After Hematopoietic Stem Cell Transplantation of a Single-center Cohort of 90 Patients with Severe Combined Immunodeficiency.

READING LIST 93 – General Content Area: Biological and Physical Hazards Encountered in the Laboratory
1. Lab Safety Matters.
2. Virus Transfer from Personal Protective Equipment to Healthcare Employees’ Skin and Clothing. Emerging Infectious Diseases.

READING LIST 94 – General Content Area: Rapid whole-genome mutational profiling using next-generation sequencing technologies.
1. Comparison of next generation sequencing technologies for transcriptome characterization.

READING LIST 95 – General Content Area: Cell Death
1. Hypoxia induces autophagic cell death in apoptosis-resistant cells through a mechanism involving BNIP3.
2. Truncated forms of BNIP3 act as dominant negatives inhibiting hypoxia-induced cell death.
3. Hypoxia-Induced Autophagy Is Mediated through Hypoxia-Inducible Factor Induction of BNIP3 and BNIPL3 via Their BH3 Domains.

READING LIST 96 – General Content Area: Genetic Associations of Cerebral Palsy
1. Mannose-binding lectin haplotypes may be associated with cerebral palsy only after perinatal viral exposure.
3. Apolipoprotein E genotype and cerebral palsy.

READING LIST 97 – General Content Area: Treatments for HIV/AIDS
2. Asia can afford universal access for aids prevention and treatment.
3. Trends in reported aids defining illnesses (adis) among participants in a universal antiretroviral therapy program: an observational study.

READING LIST 98 – General Content Area: Myosin Light Chain Kinase (MYLK) Gene Mutation Affect in Smooth Muscle Cells
1. Myosin light chain kinase is central to smooth muscle contraction and required for gastrointestinal motility in mice.
3. Chemical genetics of zipper-interacting protein kinase reveal myosin light chain as a bona fide substrate in permeabilized arterial smooth muscle.

READING LIST 99 – General Content Area: Chromosome 6 and Its Associated Diseases
1. Novel Clef7 Susceptibility Genes in Chromosome 6q.
3. The identification of chromosomal translocation, t(14; 6)(q22; q15), in prostate cancer.
READING LIST 100 – General Content Area: Early onset of autosomal dominant Alzheimer disease
1. Genetics of Alzheimer Disease.

READING LIST 101 – General Content Area: Multiplex PCR and Emerging Technologies for the Detection of Respiratory Pathogens

READING LIST 102 – General Content Area: Single Nucleotide Polymorphism (SNP) Array Analysis–2011
1. A fast and accurate method to detect allelic genomic imbalances underlying mosaic rearrangements using SNP array data.
2. SAQC: SNP array quality control.
3. Calibrating the performance of SNP arrays for whole-genome association studies.

READING LIST 103 – General Content Area: Research of BRAF Gene Related to Cancer–2011
1. Kinase-Dead BRAF and Oncogenic RAS Cooperate to Drive Tumor Progression through CRAF.
2. Distinct patterns of DNA copy number alterations associate with BRAF mutations in melanomas and melanoma derived cell lines.
3. Pharmacodynamic Characterization of the Efficacy Signals Due to Selective BRAF Inhibition with PLX4032 in Malignant Melanoma.

READING LIST 104 – General Content Area: Microarray Single Nucleotide Polymorphism (SNP) Troubleshooting–2011
1. Model-based clustering of array CGH data.
2. Application of a target array comparative genomic hybridization to prenatal diagnosis.

READING LIST 105 – General Content Area: Inflammation Activation by Proteins–2011
1. Activation of the NLRP3 inflammasome by islet amyloid polypeptide provides a mechanism for enhanced IL-1p 2 in type 2 diabetes.
3. The inflammasome: a caspase-1-activation platform that regulates immune responses and disease pathogenesis.

READING LIST 106 – General Content Area: DNA Barcoding–2011
1. Commercial Teas Highlight Plant DNA Barcode Identification Successes and Obstacles.
2. Mulational Patterns and DNA Barcode for Diagnosing Chikungunya Virus.
3. The Barcode of Life Data Portal: Bridging the Biodiversity Informatics Divide for DNA Barcoding.

READING LIST 107 – General Content Area: HERV-K and Its Correlation With Melanoma Cells–2011
1. Expression of human endogenous retrovirus K in melanomas and melanoma cell lines Cancer.
3. An endogenous retrovirus derived from human melanoma cells.

READING LIST 108 – General Content Area: Refractory Myeloma–2011
1. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease.
3. Emerging role of carfilzomib in treatment of relapsed and refractory lymphoid neoplasms and multiple myeloma.

READING LIST 109 – General Content Area: Short Tandem Repeat (STR) Technology in Forensic Community–2011
3. Generating STR profile from “Touch DNA”.

READING LIST 110 – General Content Area: Methods of Screening and Evaluation of Hepatitis C Virus–2011
2. Serial follow-up of repeat voluntary blood donors reactive for anti-hcv elisa.
3. Comparison of ribotest-actitest with histopathology in demonstrating fibrosis and necroinflammatory activity in chronic hepatitis b and c.

READING LIST 111 – General Content Area: Pharmacogenomics–2011
1. Pharmacogenomic testing: Relevance in medical practice: Why drugs work in some patients but not in others.
2. Clinical assessment incorporating a personal genome.

READING LIST 112 – General Content Area: Adrenoleukodystrophy–2011
1. Novel exon nucleotide deletion causes adrenoleukodystrophy in a Brazilian family.
2. X-linked adrenoleukodystrophy: ABCD1 de novo mutations and mosaicism.
3. Identification of novel SNPs of ABCD1, ABCD2, ABCD3, and ABCD4 genes in patients with X-linked adrenoleukodystrophy (ALD) based on comprehensive resequencing and association studies with ALD phenotypes.

READING LIST 113 – General Content Area: Quality Assurance and Quality Control of Microarray Comparative Genomic Hybridization–2011
2. Comparison of familial and sporadic chronic lymphocytic leukaemia using high resolution array comparative genomic hybridization.

READING LIST 114 – General Content Area: mFISH–2012
3. CDS-negative Blastoid Variant Mantle Cell Lymphoma with Complex CCND1/IGH and MYC Aberrations.

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Question Order Form

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Association Business

Letter from the President

Dear Colleagues,

Happy New Year! Hope you all are enjoying a successful and productive 2014!

The members of the Board of Directors, along with a substantial number of volunteers, have been busy and working diligently on several projects, including:

- The design and completion of a new AGT exhibit booth. This exhibit booth will be used and displayed in many of the upcoming annual meetings nationwide.
- An updated AGT website is now available at www.agt-info.org. I encourage all of you to take some time and visit our new updated website. Please check out the following tabs: professional development, career, ambassador program, lab directory and access information on all the labs throughout the U.S. and internationally. These and the AGT annual meeting information are among the valuable information posted on our AGT website.
- The Education Committee continues to develop educational and CEU opportunities, including webinars on the latest in the genetics field.
- The AGT annual meeting committee has completed the planning for the 39th annual meeting that will be held from June 12-14, 2014 in Louisville, Kentucky. The meeting will include a great variety of excellent workshops, scientific sessions, exhibits, sponsors, awards, and posters. A great opportunity to earn required CEUs for the whole year, and to meet friends and colleagues. I look forward to seeing all of you in Louisville!
- The AGT manual committee has been tirelessly working on the next edition of the AGT manual. More information will be provided in the AGT meeting.

These are just a few examples of what your Association is offering for its membership. This being the time of year for our membership drive, we hope that the members will see the benefits of being a member and renew their membership. I ask you to think about all the great things the Association offers to our profession and encourage you and your colleagues to become members.

As always, please feel free to contact any Board or Council of Representatives member. Our contact information can be found in the journal or at www.agt-info.org.

I thank you for being a member of AGT and your continued support to our association. I am especially thankful for all the work of the Board and Council members and volunteers.

In closing, thanks to all of you for contributing to our organization, through your membership and support. I hope we can continue to restore growth and gain more membership for the AGT. We are all ambassadors for our profession and the genetics field as a whole, and the more we encourage our colleagues to join the more our association will prosper and grow.

I am thankful to the AGT, that through my involvement, I not only gained friends and colleagues, but have grown personally and professionally, and for that I'm grateful for the opportunity and experience.

My best wishes to all of you until we meet soon in Louisville, Kentucky.

Best,
Mervat S. Ayad, BS, EMBA, CG(ASCP)CM, DLMCM, CCS
President, AGT
The 39th Annual Meeting of the Association of Genetic Technologists will challenge you with a wide variety of genetics content while you enjoy the picturesque beauty of the Commonwealth of Kentucky. Our 39th Annual Meeting boasts an outstanding program filled with a variety of workshops and education sessions that will meet your needs for biochemical genetics, cytogenetics and molecular genetic knowledge. We are also proud to host many cutting edge vendors that would really like to show you their new products and toys!

The city of Louisville, Kentucky is the home of the AGT’s 39th Annual Meeting. As you may know, Louisville is best known for being the location of the Kentucky Derby horse race. The Kentucky Derby is the first of a series of three races that makes up the Triple Crown of Thoroughbred Racing. If visiting the horse track is not your thing, you can also tour historic ‘Old Louisville.’ This Victorian neighborhood is the largest historic preservation of these types of homes and buildings in the United States. Louisville also offers a wide variety of museums and cultural centers. The Louisville Slugger Museum and Factory is a grand slam of baseball history and features a 60+ foot baseball bat! The Louisville Science Center features many interactive, hands-on exhibits and the Muhammad Ali Center has the largest collection of boxing memorabilia from this famous Louisville native. Louisville is also home to many parks and recreation areas for you to enjoy the lush landscapes of the ‘Falls of Ohio.’

Come join us in June at the 39th Annual Meeting of the Association of Genetic Technologists. We are really looking forward to seeing you at the meeting and hope you meet many new genetic contacts and friends!

Genetically Yours,

39th Annual Meeting Program Directors
Jason Yuhas, Annual Meeting Director
Adam Sbeiti, Annual Meeting Co-Director

MEETING SCHEDULE

Wednesday, June 11, 2014
8:00 a.m. – 5:00 p.m.  AGT Board Meeting

Thursday, June 12, 2014
8:00 a.m. – 12:00 p.m.  FGT Board Meeting
1:00 p.m. – 5:00 p.m.  Poster Set-Up

Pre-Conference Workshops
8:00 a.m. – 11:00 a.m.
Workshop 1: Introduction to Forensic Science
Denise Juroské Short, MS, MB(ASCP)CM, Adjunct Faculty, University of Texas, M.D. Anderson Cancer Center, Houston, Texas
Crystal Simien, BS, MB(ASCP)CM, Senior Health Professions Educator, University of Texas, M.D. Anderson Cancer Center, Houston, Texas

8:00 a.m. – 10:00 a.m.
Workshop 2: Intricacies & Interpretation of Samples for HER2 Breast Cancer Testing
Reid G. Meyer, CG(ASCP)CM, Senior Technical Specialist/Technical Specialist Coordinator, Mayo Clinic, Rochester, Minn.;
Jason Yuhas BS, CG(ASCP)CM, Education Specialist II, Division of Laboratory Genetics, Mayo Clinic, Rochester, Minn.

8:00 a.m. – 10:00 a.m.
Workshop 3: Quality Assurance in Genetics
Peggy Stupca, CG(ASCP)CM, Rochester, Minn.;
Helen M. Jenks, MT(ASCP)CG CM, Cytogenetic Technologist, Clinical Laboratory Scientist, UC Davis Health System, Sacramento, Calif.

10:30 a.m. – 12:30 p.m.
Workshop 4: FISH Analysis: Beyond Counting Dots
Shirong Wang, MS, CG(ASCP)CM, Supervisor, Quest Diagnostics, Nichols Institute, San Juan Capistrano, Calif.;
Xiaoqin Yang, MLT(ASCP)CG CM, CCS, Lead, Quest Diagnostics, Nichols Institute, San Juan Capistrano, Calif.
Association Business

10:30 a.m. – 12:30 p.m.
Workshop 5: aCGH/SNP Array Validation, Data Interpretation & Quality Control
Ming Zhao, CG(ASCP)CM, MB(ASCP)CM, Senior Health Professions Educator, The University of Texas, M.D. Anderson Cancer Center, School of Health Professions, Houston, Texas
2:00 p.m. – 4:00 p.m.
Workshop 6: FISH Testing: Reimbursement Challenges & Efficiency Opportunities
Philip N. Mowrey, PhD, MS, FACMG, CG(ASCP)CM, Chief Director, Cytogenetics, Quest Diagnostics Nichols Institute, Chantilly, Va.; Deborah W. Heritage, MS, CG(ASCP)CM, Manager, Cytogenetics Training, Quest Diagnostics Nichols Institute, Chantilly, Va.
2:00 p.m. – 4:00 p.m.
Workshop 7: From BACS/OLIGO Array to SNP Array: New Development in Perinatal & Cancer Applications
Jun Gu, MD, PhD, CG(ASCP)CM, Assistant Professor/Education Coordinator, University of Texas, M.D. Anderson Cancer Center, Houston, Texas; Clint Van Valkenburgh, PhD, Senior Clinical Sales Specialist, Central U.S.A., Affymetrix, Inc.
2:00 p.m. – 4:00 p.m.
Workshop 8: Clinical Utility & Synergy of Molecular Genetic Technologies
Douglas Blake, CG(ASCP), Clinical Field Application Scientist, Agilent Technologies, Nashville, Tenn.; Sharon Alsobrook, CG(ASCP)CM, MLS(ASCP)CM, Lead Cytogenetic Technologist, ProPath, Dallas, Texas
4:00 p.m. – 6:00 p.m.
Scientific Educators Meeting
7:00 p.m. – 9:00 p.m.
WELCOME RECEPTION IN EXHIBIT HALL, POSTER VIEWING, FGT SILENT AUCTION OPENING
Friday, June 13, 2014
7:00 a.m. – 4:00 p.m.
Scientific Sessions
8:00 a.m. – 8:10 a.m.
Welcome to the AGT 39th Annual Meeting
8:10 a.m. – 9:00 a.m.
Keynote Address
Lee H. Hilborne, MD, MPH, DLM(ASCP)CMFASCP, Professor of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, Calif.
9:00 a.m. – 9:50 a.m.
Gail H. Vance, MD, Professor and Sutphin Professor of Cancer Genetics, Indiana University, Indianapolis, Ind.
9:50 a.m. – 10:20 a.m.
BREAK IN EXHIBIT HALL/POSTER VIEWING
10:20 a.m. – 11:10 a.m.
Clinical Genome Sequencing: What’s Next in Next-Generation Sequencing?
Matthew J. Ferber, PhD, FACMG, Director of the Clinical Genome Sequencing Laboratory, Mayo Clinic, Rochester, Minn.
11:10 a.m. – 12:00 p.m.
Non-Invasive Pre-Natal Diagnosis
Charles “Buck” Strom, MD, PhD, FACMG, FAAP, HCLD, Senior Medical Director, Genetics, Quest Diagnostics Nichols Institute, San Juan Capistrano, Calif.
12:00 p.m. – 1:30 p.m.
LUNCH ON YOUR OWN
1:40 p.m. – 2:30 p.m.
Clinical Significance of the Leukemia Cell Karyotype in Children with Acute Myeloid Leukemia (AML)
Susana C. Raimondi, PhD, Director, Cytogenetics Laboratory, St. Jude Children’s Research Hospital, Memphis, Tenn.
2:30 p.m. – 3:20 p.m.
Genetic Counseling in the Era of Microarrays
Leslie Ross, MS, CGC, Genetic Counselor, Quest Diagnostics, Denver, Colo.
3:20 p.m. – 4:00 p.m.
BREAK IN EXHIBIT HALL/POSTER VIEWING
4:00 p.m. – 4:30 p.m.
Personalized Medicine & Me
Peter C. Hu, PhD, MS, MLS(ASCP)CMCGCMBCMG, Program Director, University of Texas, M.D. Anderson Cancer Center, Houston, Texas
4:30 p.m. – 5:20 p.m.
Health & Safety
Mervat Ayad, BS, EMBA, CG(ASCP)CM, DLM(ASCP), CCS, Director, Laboratory Operations, Quest Diagnostics at Nichols Institute, San Juan Capistrano, Calif.
5:30 p.m. – 7:30 p.m.
AGT JOB FAIR
Saturday, June 14, 2014
7:00 a.m. – 8:00 a.m.
BUSINESS MEETING BREAKFAST
Scientific Sessions
8:00 a.m. – 8:10 a.m.
Opening Remarks
8:10 a.m. – 9:00 a.m.
Gordon W. Dewald Lecture: Clinical Laboratory Education in Diagnostic Genetics – The Road to a Brighter Future in Health Care
Vicki L. Hopwood, MS, CG(ASCP)CM, Assistant Professor, Director, Cytogenetic Technology Program, University of Texas, M.D. Anderson Cancer Center, Houston, Texas
9:00 a.m. – 10:40 a.m.
Abstract Platform Presentations & Student Abstract Award Winner Abstract Presentation
10:40 a.m. – 11:20 a.m.
BREAK IN EXHIBIT HALL/POSTER VIEWING
11:30 a.m. – 12:20 p.m.
Informed Consent for Whole Genome Sequencing
Katherine S. Hunt, PhD, MS, CGC, Assistant Professor in Medicine, Genetic Counselor, Mayo Clinic, Scottsdale, Az.
12:20 p.m. – 1:45 p.m.
LUNCH ON YOUR OWN
12:20 p.m. – 1:45 p.m.
UCONN LUNCHEON
1:45 p.m. – 2:35 p.m.
Miscarriages, Cell Morphology & Villi Formation: Detecting High Abnormality Percentages in POCs
Philip J. Hardy, M. Clin Cyto, B.Bus Ltd., Perth, Western Australia
2:35 p.m. – 3:25 p.m.
Targeted Therapies for Solid Tumors and Companion Diagnostics
Dianne Keen-Kim, PhD, FACMG, Executive Director, Cytogenetics, Genoptix Medical Laboratory, Carlsbad, Calif.
3:25 p.m. – 3:30 p.m.
Silent Auction Winners Announced
3:30 p.m. – 3:45 p.m.
BREAK
3:45 p.m. – 4:35 p.m.
Topical TBD
Kara Goodin, MD, Clinical Geneticist, Assistant Professor of Pediatrics, University of Louisville School of Medicine, Louisville, Ky.
4:35 p.m. – 5:25 p.m.
Overview of the New AMA Molecular Pathology CPT Codes
V.M. Pratt, PhD, FACMG, Director, Pharmacogenetics Laboratory, Indiana University School of Medicine, Indianapolis, Ind.
6:00 p.m. – 7:00 p.m.
ANNUAL AWARDS RECEPTION
7:00 p.m. – 11:00 p.m.
ANNUAL AWARDS BANQUET & DANCE

The Journal of the Association of Genetic Technologists 40 (1) 2014 47
REGISTRATION INFORMATION

Early Registration Deadline – Postmarked by April 1, 2014

Regular Registration – April 2-May 16, 2014

On-site Registration – After May 16, 2014

Registrations processed on-site may cause a delay at the time you check in at the AGT Annual Meeting registration desk. If you need to register after May 16, please bring your completed registration form and payment directly to the meeting.

**Annual Meeting Registration (Friday and Saturday) Includes:**
- Name badge, Final Program, online access to presentations
- Continental breakfast and refreshment breaks
- Welcome Reception
- Awards Reception & Banquet

**Single-Day Registration Includes:**
- Name badge, Final Program, online access to presentations
- Any meal functions scheduled for that day

*Please note that continental breakfast and lunch are not provided for Pre-Conference Workshops on Thursday, June 12.*

**Registration Confirmation**
For registrations received prior to May 16, AGT will send a confirmation letter by e-mail or U.S. mail. When you receive your confirmation letter, please check the spelling of your name, address and the events for which you are registered to ensure that they are correct. The information on your confirmation letter will be the information used for your name badge and event tickets. If there is an error, please contact Autumn Menefee at the AGT Executive Office at (913) 895-4764. If you do not receive a confirmation letter within three weeks of registering, please contact our office to confirm receipt of your registration.

**Registration Cancellation Policy**
Written notice of cancellation postmarked on or before May 16 will be refunded minus a $50 processing fee (to be processed after the annual meeting). No refunds will be issued after May 16, 2014. Substitutions of registrants are allowed. AGT will be distributing a roster of names of attendees who pre-register for the meeting. To be included on the roster, your registration must be received at the AGT Executive Office by May 16, 2014.

**Questions?**
Contact the AGT Executive Office at:
- P.O. Box 19193
- Lenexa, KS 66285 USA
- 913-895-4605
- Fax: 913-895-4652
- Email: agt-info@goAMP.com
- Web Site: www.agt-info.org

**Hotel Reservations**
Louisville Marriott Downtown
280 W. Jefferson St.
Louisville, KY 40202
502-627-5045

Rate: $163 plus tax per night single/double
Room rate includes wireless in-room Internet and fitness center access.
**Reservation Deadline: May 19, 2014**
Make reservations online at
https://resweb.passkey.com/Resweb.do?mode=welcome_gi_new&groupId=20060442 or call 1-800-866-9432.
STEP 1: Name Badge & Roster Information

First Name  Last Name

Name Preferred on Name Badge

Company/Institution

Business Address

City State/Province  Zip/Postal Code  Country

Business Phone  Cell Phone (to be used in case of emergency)  E-mail

Specific requests (subject to availability)

☐ Gluten Free  ☐ Vegetarian  ☐ Vegan  ☐ Other (describe allergies here)

☐ I am a new AGT member since June 2013.

☐ This is the first AGT meeting that I have attended.

☐ Check here if the address information above is different from what appears on your AGT mailing label.

STEP 2: Join AGT!

Join AGT now and register for the Annual Meeting for the member price below. Membership will run through December 31, 2015.

☐ Full - $95  ☐ Emeritus - $40  ☐ Student - $35

STEP 3: Registration Fees

Full & Single-Day Conference Fees

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Single-Day Registration Only:

Please indicate day attending:

☐ Friday, June 13  ☐ Saturday, June 14

STEP 4: Pre-Conference Workshops – Thursday, June 12, 2014

Please ensure that the workshops and seminars you select do not overlap! Space is limited and will be assigned on a first-come, first-serve basis.

Workshop 1: Introduction to Forensic Science
8:00 a.m. – 11:00 a.m.

☐ $75 AGT Member  ☐ $95 Non-Member

Workshop 2: Intricacies & Interpretation of Samples for HER2 Breast Cancer Testing
8:00 a.m. – 10:00 a.m.

☐ $50 AGT Member  ☐ $70 Non-Member

Workshop 3: Quality Assurance in Genetics
8:00 a.m. – 10:00 a.m.

☐ $50 AGT Member  ☐ $70 Non-Member

Workshop 4: FISH Analysis: Beyond Counting Dots
10:30 a.m. – 12:30 p.m.

☐ $50 AGT Member  ☐ $70 Non-Member

Workshop 5: aCGH/SNP Array Validation, Data Interpretation & Quality Control
10:30 a.m. – 12:30 p.m.

☐ $50 AGT Member  ☐ $70 Non-Member

Workshop 6: FISH Testing: Reimbursement Challenges & Efficiency Opportunities
2:00 p.m. – 4:00 p.m.

☐ $50 AGT Member  ☐ $70 Non-Member

Workshop 7: From BACS/OLIGO Array to SNP Array: New Development in Perinatal &Cancer Applications
2:00 p.m. – 4:00 p.m.

☐ $50 AGT Member  ☐ $70 Non-Member

Workshop 8: Clinical Utility & Synergy of Molecular Genetic Technology
2:00 p.m. – 4:00 p.m.

☐ $50 AGT Member  ☐ $70 Non-Member
### AGT Registration Form, continued

#### STEP 5: Guest Registration
Are you bringing a guest to the Annual Meeting? Consider purchasing special events tickets so that your guest can join you at the following functions.

- **Welcome Reception Guest**  \( \text{(\_\_ persons x $35)} \)
- **Awards Reception Guest**  \( \text{(\_\_ persons x $45)} \)

Guest Name: __________________________________________

Please note: Each attendee will receive one ticket to each event at no additional cost as part of the registration fee.

#### STEP 6: Total Fees

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#### STEP 7: Payment Information

Payment is due in full with your registration form. Fees are based upon the postmark date. Payment may be made by credit card or checks in U.S. funds drawn on a U.S. bank.

Please make checks payable to the Association of Genetic Technologists (AGT) – Federal Tax ID #94-2668057

☐ Check enclosed
☐ Credit Card
  ☐ MasterCard  ☐ VISA  ☐ American Express  ☐ Discover

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Signature

Name as it appears on the card (please print)

Cardholder Phone Number

#### STEP 8: Send Your Registration
To register, complete the registration form and return it, along with the appropriate payment, to:

- **Mail:**
  AGT Executive Office
  P.O. Box 19193
  Lenexa, KS 66285

  Overnight mail only
  AGT Executive Office
  18000 W. 105th Street
  Olathe, KS 66061

- **Fax:** (913) 895-4652
  Registration forms and payment information can be faxed.

- **Online Registration:**
  Registrations can be completed and submitted online via the AGT web site at www.agt-info.org.
  A link to online registration is located on the Annual Meeting page.

### Cancellations

All fees must be paid in U.S. dollars, with checks drawn in U.S. funds from U.S. banks. In the event of cancellation prior to or on May 16, registration fees will be returned, less a $50 processing fee. All refunds on cancellations will be issued after the meeting. Substitutions are allowed. There will be no refunds issued or substitutions allowed after May 16.
SAVE THE DATE
April 30 – May 2, 2014

CLC Meeting and Registration Information
Visit www.asclsmn.org

CLC Meeting Location:
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Association of Genetic Technologists – 2013-2015

The Association of Genetic Technologists (AGT), originally founded in 1975 as the Association of Cytogenetic Technologists, serves to:

- promote the scientific and professional development of all areas of genetics;
- foster the exchange of information between those interested in genetics;
- encourage cooperation between those persons actively or formerly engaged in genetics; and
- stimulate interest in genetics as a career.

AGT has over 1,300 members. Membership is open to all who are employed or interested in genetics. All regular members are entitled to hold office, vote in elections, attend all AGT meetings, and receive The Journal of the Association of Genetic Technologists and access the AGT International Online Membership Directory.

Visit AGT’s Website at http://www.AGT-INFO.org
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Pittsburgh Cytogenetics Lab  
300 Haliet St., Room 1233  
Pittsburgh, PA 15213  
412-641-4882  
skochmar@upmc.edu
The AGT Molecular Biology Techniques Review Guide
Is now available through the AGT Executive Office

Author: Judy Brown, PhD, CLSp(CG), CLSp(MB), Contributors: Ellen Drieghe, BS and Jaclyn Gordon, BS, Diagnostic Genetic Sciences Program, University of Connecticut, Storrs, CT

The Association of Genetic Technologists’ Molecular Biology Techniques Review guide was written by a technologist for technologists studying for a credentialing examination in molecular biology. The study guide presents experimental theories, specimen requirements, quality control procedures, troubleshooting techniques and self-assessment questions for molecular biology techniques used in full-service laboratories. Techniques outlined include sample collection, nucleic acid isolation, nucleic acid manipulations (restriction enzyme digestions, cloning, labeling), electrophoresis, amplification and blotting techniques, sequencing, summarizing and reporting results, and laboratory practice. The study guide concludes with an ample list of references. This is a valuable and helpful resource for any technologist and has received high praise for its effectiveness in reviewing the content on the credentialing examination.

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Please return to: AGT Executive Office, P.O. Box 15945-288, Lenexa, KS 66285; Fax (913) 895-4652; Email: agt-info@goamp.com
The AGT Cytogenetics Laboratory Manual
Is now available through the AGT Executive Office

ORDER YOUR COPY TODAY!

Margaret J. Barch (Editor), Turid Knutsen (Editor), Jack Spurbeck (Editor)
This third edition includes: an expanded FISH chapter; information and protocols for breakage studies; coverage of computer imaging, regulation, and the molecular aspects of leukemia; and chromosome spreading. Over 200 step-by-step protocols are also presented throughout the text.

Only available in PDF format on a USB drive (June 1997)

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Please return to: AGT Executive Office, P.O. Box 19193, Lenexa, KS 66285 or Fax to 913-895-4652
The second edition of *The Cytogenetic Symposia*, published in 2005, consists of an introduction, briefly outlining the development of the practice of cytogenetics, from the seminal work of Tijo and Levan in 1956 to the current partnership of cytogenetics and molecular genetics. The succeeding chapters, written by cytogenetic technologists, PhDs, and medical doctors from the United States and Canada, provide up-to-date information on a broad range of topics in both cytogenetics and molecular cytogenetics. Many chapters now include molecular information reflecting the increased recognition of diagnostic complementation of these arenas. Each chapter includes a set of multiple choice questions and most chapters contain a glossary. The answers for chapter questions have been placed in an appendix. The intent of *The Cytogenetic Symposia* is to offer a thorough, but condensed overview of the field. This publication is an excellent resource for individuals preparing for the NCA cytogenetics certification examination. Use of references cited in each chapter will lead interested parties to more detailed information.

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The Professional Organization for Genetic Technologists

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The AGT Annual Meeting
Journal Club and “Test Yourself”
Cytogenetics Lab Manual, Symposia, Molecular Review Guide and free access to the salary survey

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Publications such as our peer-reviewed *Journal of the Association of Genetic Technologists*, Online access to the AGT International Membership Directory, and E-news updates
Government and legislative updates
Networking opportunities that include Facebook, and the AGT Forum

Visit our website for details on our upcoming membership contest!

www.agt-info.org
New Membership Application

Please check the membership category you are applying for:

☐ Regular Membership $95  ☐ Emeritus $40
☐ Student Membership $35  ☐ Collaborative $40

Please complete all information below. Please indicate in the check box which address you prefer for mail distribution and directory publication.

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☐ Home Address: _______________________________________________________________________________________________________

City, State, Zip: _________________________ Phone: ___________________________

☐ Business Name: _______________________________________________________________________________________________________

Business Address: _______________________________________________________________________________________________________

City, State, Zip: _________________________ Phone: ___________________________

Fax: ___________________________________________________________________________ Preferred Email: ___________________________________________________________________________

The supplied address will be published in the directory unless otherwise specified.

☐ Do not publish my address in the AGT Membership Directory

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Referred By __________________________________________________________________________ Membership # ___________________________

Did you use a different name last year:  ☐ Yes  ☐ No

Former Last Name ___________________________ First Name ___________________________ MI __________________

Position: (check one)  ☐ Director  ☐ Supervisor  ☐ Technologist  ☐ Lab Manager

☐ Head (Lead, Core) Technologist  ☐ Tissue Culture Tech.  ☐ Education Coordinator  ☐ Other

Principal area of Genetics: (check one)  ☐ Biochemical  ☐ Cytogenetics  ☐ Molecular  ☐ Other

Appropriate years experience in Genetics:  ☐ under 2  ☐ 2-4  ☐ 5-7  ☐ 8-10  ☐ 11-15  ☐ 16-20  ☐ 21-30  ☐ over 30

NOTICE: OUR MAILING LIST IS MADE AVAILABLE TO OTHER ORGANIZATIONS AND/OR COMPANIES. IF YOU WISH YOUR NAME NOT TO APPEAR ON THESE LISTINGS, PLEASE CHECK HERE: ☐

Journal Hard Copy Order: Although The Journal of Genetic Technologists is available online to ALL MEMBERS, only North American members can elect to receive a hard copy via regular mail for an additional fee of $25. This fee covers four issues. If you are a North American resident and would like a hard copy of the Journal, please remit the additional fee with your membership application by checking the box and adding the amount to your total payment. ☐ $25 fee

Mail application form and appropriate fee for membership in correct U.S currency. Money order or check in U.S. funds drawn on a U.S. bank only. CHECKS DRAWN ON INTERNATIONAL BANKS WILL NOT BE ACCEPTED. Make checks payable to Association of Genetic Technologists. For your convenience, you may pay by credit card. Applications received after September 15 are applied toward the next membership year. NOTE: Membership expires on December 31 of each year.

☐ VISA ☐ MasterCard Account No. ___________________________ Exp. Date ___________________________

☐ AMEX ☐ Discover Signature ___________________________

MAIL APPLICATION AND FEE TO:

Association of Genetic Technologists
P.O. Box 19193
Lenexa, KS 66285
Phone: 913-895-4605
FAX: 913-895-4652
2014 Scientific Meeting Schedules

If you know of a relevant meeting, please send information to Jun Gu, Public Relations Director at jungu@mdanderson.org. We are always looking to improve AGT's annual meeting. If you attend a meeting and see something you think would enhance our meeting, please email your ideas to Denise Anamani, Annual Meeting Director, (denise.anamani@uconn.edu) and Jun Gu.

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Job placement ads are online at //www.AGT-INFO.org
Information For Authors

The Journal of the Association of Genetic Technologists is pleased to consider manuscripts that describe experience with cytogenetics, molecular genetics, or biochemical genetics and the application of these disciplines.

Submitted manuscripts must be typed, preferably double-spaced, using a 12 point font and 1” margins. In addition to the original, three copies of the manuscript and camera-ready illustrations must be submitted to the editor-in-chief. Items to be italicized or enhanced (bold, underlined) should be clearly indicated. The conversion factor for print equivalency is as follows: two double-spaced typed pages equal approximately a one-half typeset page.

Authors may supply the material on a 3½” disk, preferably in Microsoft Word, WordPerfect, or ASCII format, along with the hard copy. Macintosh disks are also acceptable, but conversion costs will be assessed accordingly to AGT and a delay in processing may occur. Materials may alternatively be supplied to the editor via email at the address shown on inside front cover. Email submission is preferred.

Illustrations must be original photographs, computer-generated digitized files (preferably saved as a .tif, .eps, or .bmp file), or black and white line drawings, professionally prepared. The cost of separating and printing color photographs or illustrations will be charged to the author. Photographs must be properly identified on the back, including the author’s name, title of article, and top direction. A ball point pen should not be used for labeling. The affixing of a typewritten label to the illustration or table will prevent damage.

Notation & References

Authors’ titles must be accompanied by a position description of less than 15 words, which will be printed with the article.

Textual citations to the referenced literature should be parenthetically noted by author’s surname followed by year of publication, and arranged chronologically and then alphabetically, as demonstrated in the following example: (Lese and Ledbetter, 1998; Reilly, 1998a; Morgan et al., 1999). In situations with more than two authors, the first author’s surname should be followed with et al. When references are made to more than one paper published in the same year by the same author, a lower case a, b, etc. should be appended to the date of publication and should be included in both textual citations and the reference list.

References should be listed completely at the end of the paper in alphabetical order by surname of first author, and then by year of publication. When more than one publication appears with the same first author, listings will be alphabetized by the first varying co-author. Irrespective of the number of authors, et al. should not be used in the reference list. Journal titles should be abbreviated according to Index Medicus and book titles should be italicized. Use the following format for references:

Journal Article

Book Chapter

Book

All references should be complete. Accuracy is the responsibility of the authors. Only published articles and those in press may be included in the reference list. If necessary, unpublished data and submitted manuscripts should be cited parenthetically within the text.

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Reprints are produced on 60# white offset paper, saddle-stitched (unless under four pages), and will appear exactly as they do in the journal. Price is based on article length, quantity ordered, and color requirements. Orders are not processed until payment is received. Once payment is received, allow four weeks for printing and shipping. Prices quoted include shipping by UPS ground; expedited shipping is available at an additional charge. Journal copies can be purchased by AGT members for $5/each and by non-members for $25/each, if copies are available.

Please forward reprint orders or questions regarding price quotations to the AGT Executive Office (see inside front cover for address).