The Human Genetics Laboratory Receives Accreditation from College of American Pathologists (CAP)

Renée Fordyce-Boyer, M.S., CLSp(CG)

The University of Nebraska Medical Center (UNMC) Human Genetics Laboratory, Omaha, Nebraska, has been awarded an accreditation by the Commission on Laboratory Accreditation of the College of American Pathologists (CAP), based on the results of a recent on-site inspection.

The laboratory’s director, Dr. Warren Sanger, was advised of this national recognition and congratulated for the “excellence of the services being provided”. UNMC’s Human Genetics Laboratory has been accredited by CAP for over 30 years, and is one of 6,000 CAP-accredited laboratories nationwide.

The CAP Laboratory Accreditation Program, begun in the early 1960s, is recognized by the federal government as being equal to or more stringent than the government’s own inspection program.

During the CAP accreditation process, inspectors examine the laboratory’s records and quality control of procedures for the preceding two years. CAP inspectors also examine the entire staff’s qualifications, the laboratory’s equipment, facilities, safety program and records, as well as overall management of the laboratory. This stringent inspection program is designed to specifically ensure the highest standard of care for the laboratory’s patients.

The College of American Pathologists is a medical society serving nearly 16,000 physician members and the laboratory community throughout the world. It is the world’s largest association composed exclusively of pathologists and is widely considered the leader in laboratory quality assurance. The CAP is an advocate for high-quality and cost-effective medical care.

Clinical Genetic Evaluation of Autism

G. Bradley Schaefer, M.D. and Richard E. Lutz, M.D.

Autism spectrum disorders (ASD) are a collection of neurobehavioral conditions that share in common abnormalities of socialization and communication. These disorders exhibit complex inheritance with marked etiologic heterogeneity. ASDs are classically described as manifesting multifactorial inheritance. As in many multifactorial disorders, better elucidation of the contributing factors has revealed numerous unifactorial genetic etiologies.

Clinical geneticists are often asked to evaluate patients with ASD in reference to questions about etiology and recurrence risk. Currently, there is no clear consensus on the diagnostic approach to such patients. Published data suggests a diagnostic yield of 20% by history and physical examination alone. Additional studies including neuroimaging, EEG, Fragile X testing, and metabolic screening have been reported to increase this yield by a meager 2%.

Recent advances in cytogenetic, molecular genetic, and metabolic technologies have significantly expanded the diagnostic armamentaria available for evaluating such patients. Multiple anecdotal reports have noted the association of many of these newer tests in association with a small number (often single cases) of patients with ASD. To date, no specific battery of tests has been purported as the ideal set of autism tests. Likewise, it is not clear what the overall diagnostic yield for these tests is - either collectively or individually.

We have developed a systematic neurogenetic evaluation scheme designed to try and determine the etiology of ASD in patients referred for clinical genetic consultation (Table 1). This scheme is a four tiered system of evaluations that prioritizes tests in the higher (earlier) tiers based upon the projected yield and ease of accomplishing the test. We have reviewed our patient data for autism evaluations for the last 3 years using this applied scheme. Review of this data confirms previous observations that approximately 20% of patients

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Clinical Genetic Evaluation of Autism (cont.)

with ASD have a recognizable etiology based on history and physical alone. Application of our tiered evaluation scheme provided an identifiable etiology in almost an additional 20%. Thus, the overall diagnostic yield for ASD approaches 40%. This represents a significant increase in the diagnostic yield reported just a few years ago. Given the implications of these diagnoses on recurrence risk and associated medical conditions, an aggressive neurogenetic evaluation of all persons with ASD appears warranted.

Table 1: Tiered Evaluation for Autism

Initial evaluation to identify known syndromes or associated conditions:

- Dysmorphology / Clinical genetics
  - Should include Woods lamp evaluation
  - If diagnosis suspected => targeted testing
- ‘Standard’ metabolic screen
  - Urine MPS, OA,
  - Serum lactate, AA, ammonia, acyl-carnitine profile
- Sensory screening
- EEG
- TORCH titers – if clinical indicators present

Second tier:
- Prometaphase chromosomes
- Brain MRI
- DNA for Fragile X
- Comparative genomic hybridization (microarray) includes:
  - 15 interphase duplication / deletion
  - 17q deletion / duplication
  - Subtelomeric FISH panel

Third tier:
- MECP-2 gene testing
- 15 methylation
- Serum and urine uric acid
  - If elevated, HgPRT and PRPP superactivity testing.
  - If low, purine / pyrimidine panel (uracil excretion, xanthine, hypoxanthine).

Comparative Genomic Hybridization (CGH) Microarray Technology for the Detection of Chromosomal Imbalance

Diane Pickering, M.S., CLSp(CG), Bhavana Dave, Ph.D., Denae Golden, B.S., CLSp(CG), Kim Wiechman, B.S., CLSp(CG), and Warren Sanger, Ph.D.

The ability to detect subtle chromosome aberrations has improved in our laboratory over previous decades due to better resolution of G-banded metaphase chromosomes and the development of FISH procedures to help identify specific sub-microscopic deletions and duplications. These improvements have led to a significant increase in the detection rate of chromosome imbalances in patients with mental retardation and/or congenital anomalies. Most recently, the Human Genetics Laboratory has incorporated chromosomal microarray, a modified CGH procedure, that tests many chromosome regions in one assay. The following two microarrays are utilized in our laboratory for clinical applications:

- The Constitutional Microarray 400 is designed to test for deletions and duplications in a large number of chromosomal regions known to be associated with specific syndromes.
- The 2600 is a high-resolution array (approximately 1 MB) employed to further delineate previously identified breakpoints, confirm constitutional array results, and interrogate chromosome regions not represented on constitutional array.

Advantages of CGH Microarray

- Comprehensive screen of several “critical” chromosome regions.
- Eliminate numerous single-FISH tests, particularly sub-telomere panel.
- High resolution (<2MB)
- Reliably detects chromosome duplication in addition to deletion.

Limitations of CGH Microarray

- Does not detect balanced chromosome abnormalities, mosaicism and gene mutations
- Parental studies may be needed in some cases to resolve the variable nature of certain loci represented on the microarray.

Overall, the CGH microarray procedure is clinically indicated for patients with moderate to severe cognitive delays with or without dysmorphic features. The overall detection rate of chromosomal imbalance in this clinical category is 10-15%.
The Utility of FISH for Diagnosis and Monitoring of Malignancies

Warren G. Sanger, Ph.D. and Michele Wiggins, B.A., CLSp(CG)

Fluorescence in situ hybridization (FISH) is becoming continually more utilized in the area of oncology. FISH can be used to confirm specific diagnostic chromosome abnormalities, to identify abnormalities when cytogenetics is not available or when malignant cells are not undergoing division, to monitor disease progression and to determine remission status. The panel of probes which are utilized in the area of oncology is continuously changing. The philosophy of our Human Genetics Laboratory is that of utilizing only those probes which are useful in confirmation of a diagnosis and/or determining prognosis for a specific malignancy. The following is a list of diseases in which FISH can be used in the diagnosis and monitoring the malignancies:

**Hematology & Oncology**

**CML**  
BCR/ABL [t(9;22) / LSI 9q34]

**ALL**  
TEL/AML [t(12;21)]  
TEL [12p13]  
Hypermidiody  
BCR/ABL [t(9;22)] / LSI 9q34  
MLL [11q23]

**CLL**  
12CEP  
D13S319 [13q14 / 13q34]  
ATM [11q23]  
IgH translocation  
p53 [17p13.1]

**MDS**  
EGR-1 [5q31]  
8CEP  
7CEP / D7S486 [7q31]  
D20S108 [20q12]

**MM**  
D13S319 [13q14 / 13q34]  
IgH translocation  
IgH/CCND1 [t(11;14)]  
IgH/FGFR [t(4;14)]  
IgH/MAF [t(14;16)]  
p16 [9p21]  
p53 [17p13.1]  
Hypermidiody [CEP 9/11/15]

**AML**  
7CEP  
8CEP  
MLL [11q23]  
ETO/AML1 [t(8;21)]  
PML/RARA [t(15;17)]  
CBFB [16q22]

**Lymphoma Probes**

**ALK** [(2p23 & variants)]

**IgH / MYC / 8CEP** [t(8;14)]

**IgH / CCND1** [t(11;14)]

**IgH / BCL2** [t(14;18)]

**Lymphoma Probes (cont.)**

**IgH / MALT** [t(14;18)]

**IgH** [14q32 abnormalities]

**BCL6** [3q27]

**CMYB** [6q23]

**CMYC** [8q24]

**CCND1** [11q13]

**TCR** [14q11]

**MALT1** [18q21 / t(11;18)]

**BCL2** [18q21]

**BCL6** [3q27]

**CMYB** [6q23]

**CMYC** [8q24]

**CCND1** [11q13]

**TCR** [14q11]

**MALT1** [18q21 / t(11;18)]

**Neuroblastoma**

**NMYC** [2p24.1]

**1p36 deletion**

**EGFR** [7p12]

**Rhabdomyosarcoma**

**FKHR** [13q14]

**Sarcoma**

**Ewing** [t(11;22) & variants]

**Liposarcoma** - LSI CHOP [12q13]

**Synovial** - SYT [18q21] [t(X;18)]

**Bladder Cancer Panel**

**CEP3**

**CEP7**

**CEP17**

**p16** [9p21]

**Neurological Cancer Probes**

**1p36 / 1q25**

**19q13 / 19p13**

**Breast Cancer**

**HER2/neu** [17q12]

The composition of these probe panels are still evolving, and our intent is to continue to utilize only those probes which are known to have diagnostic or prognostic management value.

Our laboratory strives to provide “state-of-the-art” laboratory services. We encourage feedback regarding any new services you would like offered and/or any recommendations as to how we can improve our services. Also, if you would like any particular issues addressed in future newsletters, please let us know. We appreciate having the opportunity to provide genetics services for you and your patients.
SPECIMEN SHIPPING & HANDLING

1. Notify HGL in advance of specimen arrival and/or to arrange for specimen pickup (pickup provided within the Omaha-Council Bluffs metropolitan area only). Outside of this area, the transport of specimens by overnight express courier service is available and will be paid by HGL. Specimens should arrive within 24 hours of collection.

2. Specimens should be collected under sterile conditions and transported at room temperature unless otherwise indicated. Special arrangements are required if extremes in temperatures or if extended transport times are anticipated. DO NOT FREEZE.

3. Label specimen with patient’s full name, date of birth, and date/time of specimen collection.

4. Send a completed cytogenetics patient information form with the specimen. Include the patient’s name, date of birth, diagnosis, physician’s name and phone number, billing/insurance information and tissue type. If these forms are not available, please call us at (402) 559-5070, and we will fax these to you, or they can be retrieved by accessing our website.

More information is available on our website:  www.unmc.edu/services/geneticslab