The UNMC Human Genetics Laboratory Celebrates 30 Years of College of American Pathologist Accreditation
Renée Fordyce-Boyer, M.S., CLSp(CG)

Thirty-five years ago the University of Nebraska Medical Center campus was different from today. There were more open spaces, parking was easier and the buildings weren’t so tall. In 1969, the UNMC Human Genetics Laboratory was located in the basement of The Nebraska Psychiatric Institute with a couple of technologists. Cytogenetic analysis was performed on unbanded chromosomes and limited to numerical and structural abnormalities. By 1974, the laboratory had moved to Poynter Hall and the offices to a small house on 41st Street. Genetics was turning into a fast-changing science. The discovery of G-banding and Q-banding enabled Cytogeneticists to discover deletions, additions and subtle chromosome translocations; abnormalities that were impossible to distinguish before. In 1980, Dr. Warren Sanger became the Director of the Human Genetics Laboratory and the Genetic Semen Bank. Technical staff continued to grow to keep up with the rapid advances in genetic technology and the department expanded to an annex lab in Swanson Hall. While the technologists continued to process and analyze increasing numbers and types of diagnostic tests, Dr. Bruce Buehler arrived and the lab joined The Meyer Rehabilitation Institute. By 1985, the second floor of the Hattie B. Munroe Pavilion was remodeled and the laboratory moved into their current home. In 1995, the Genetic Semen Bank was closed and that lab space was converted to Fluorescence in situ Hybridization (FISH) technology. There are now 32 NCA-certified Cytogenetic Technologists and 16 other Technologist and staff, who culture and analyze approximately 7000 specimens a year. The laboratory performs cytogenetics, FISH, methylation studies, Comparative Genomic Hybridization (CGH), and microarray analyses. The Laboratory Director is still Dr. Warren Sanger and the Associate Directors are Dr. Bhavana Dave and Dr. Julia Bridge, who are all ACMG Board Certified Cytogeneticists. The laboratory has been CLIA and CAP accredited since 1974 and is celebrating those past 30 years by looking forward. The lab utilizes state-of-the-art equipment and technology, and encourages continuing education for all staff members to provide patients and physicians with the highest quality genetic services available.

Neurological FISH Panel
Michele Wiggins, B.A., CLSp(CG) & Mari Nelson, B.S., CLSp(CG)

There are continual advances toward the development of new probe panels for various diseases detectable by fluorescence in situ hybridization (FISH). Chromosomal deletions of the 1p36 and 19q13 regions as well as amplification of the N-myc oncogene are characteristic molecular features of certain solid tumors. A neurological FISH panel is now available which includes probe sets useful in identifying these genetic alterations. Diffuse gliomas often exhibit deletions involving the 1p36 and 19q13 regions. The LSI 1p36/LSI 1q25 and the LSI 19q13/19p13 Dual-Color Probe sets are useful in detecting these deletions. Another probe set combining the LSI N-myc (2p24.1) probe with a chromosome 2 centromere control is useful in detecting amplification of the N-myc oncogene which is commonly observed in neuroblastomas. These FISH tests may be performed on touch preparations from fresh or frozen tumor sections or on paraffin embedded tumor tissue.

Specimen Shipping & Billing Arrangements
Supplies, all local and long-distance courier transport services are provided by the Human Genetics Laboratory at no-charge to our clients or patients and can be obtained by telephoning our laboratory at (402) 559-5070. Details for specimen collection and shipping may also be obtained on our website at: www.unmc.edu/services/geneticslab. Our costs are competitive with other genetic laboratories around the country. Patient or third parties can be billed for services directly, or we can bill a client, hospital, or physician, depending upon the preference of the referring source. Any questions will be handled in a timely fashion by telephoning our experienced staff at (402) 559-5070.
Biochemical Diagnostic Studies for Sjögren-Larsson Syndrome, X-Linked Ichthyosis, Gaucher Disease, Multiple Sulfatase Deficiency, & Neutral Lipid Storage Disease
Dr. William Rizzo

DIAGNOSTIC TESTING FOR NEURO-ICHTHYOTIC SYNDROMES

Patients with neuro-ichthyotic syndromes exhibit ichthyosis (dry, scaly skin) and neurologic symptoms, such as mental retardation, seizures, spastic diplegia or ataxia. The Table below lists the most commonly recognized neuro-ichthyotic syndromes and their clinical features. Although there are certain clinical features that would suggest a particular diagnosis among these diseases, the definitive diagnosis requires specific tests to demonstrate the gene mutation or biochemical abnormality. Because mutations in each of these diseases are numerous, the most cost effective approach is to use a biochemical test, such as enzyme analysis, to confirm the diagnosis.

We offer a panel of biochemical tests to diagnose the neuro-ichthyotic syndromes. These are listed in the Table.

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>CLINICAL FEATURES</th>
<th>BIOCHEMICAL DEFECT</th>
<th>DIAGNOSTIC TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sjögren-Larsson syndrome</td>
<td>Congenital ichthyosis, mental retardation, spastic diplegia</td>
<td>Deficient fatty aldehyde dehydrogenase</td>
<td>Fatty aldehyde dehydrogenase</td>
</tr>
<tr>
<td>Multiple sulfatase deficiency</td>
<td>Ichthyosis onset in infancy-childhood, mental retardation, course facies, hepatosplenomegaly, ataxia</td>
<td>Deficient activity of many sulfatase enzymes due to impaired post-translational modification</td>
<td>Arylsulfatase C &amp; other sulfatases</td>
</tr>
<tr>
<td>Infantile Gaucher disease (type 2)</td>
<td>Congenital ichthyosis, hepatosplenomegaly, seizures, anemia, thrombocytopenia</td>
<td>Deficient glucocerebrosidase</td>
<td>Glucocerebrosidase</td>
</tr>
<tr>
<td>Neutral lipid storage disease</td>
<td>Congenital ichthyosis, mental retardation, hepatosplenomegaly, myopathy, vacuolated eosinophils</td>
<td></td>
<td>Triglyceride accumulation</td>
</tr>
</tbody>
</table>

DIAGNOSTIC TESTING FOR X-LINKED ICHTHYOSIS

X-linked Ichthyosis is caused by deficiency of arylsulfatase C (steroid sulfatase). Most mutations are large deletions of the STS gene that can be detected by FISH, a diagnostic test offered by our cytogenetics lab. A small proportion of X-linked ichthyosis patients have non-deletion mutations that results in arylsulfatase C deficiency. These patients are best diagnosed by measurement of enzyme activity. X-linked ichthyosis is not usually associated with neurologic symptoms. Rarely, patients with large microdeletions exhibit neuro-ichthyosis symptoms, in which case testing by FISH or enzymatic methods would be appropriate.

All diagnostic tests are performed on cultured skin fibroblasts. If a specific test is requested for diagnosing one disease, such as Sjögren-Larsson syndrome, we will assay the definitive enzyme together with a control enzyme. Alternately, if the referring physician or laboratory is not sure about a specific disease, it may be useful to perform the entire neuro-ichthyosis panel of tests. Physicians and health care providers are encouraged to telephone or contact Dr. Rizzo by e-mail (wrizzo@unmc.edu) to discuss a particular patient prior to sending specimens. In cases where the patient has no insurance coverage and limited ability to pay for the testing, we urge you to contact us directly to discuss the testing. Our greatest desire is to properly diagnose your patient.

It has been our experience that about one-half of patients referred for testing have normal test results, despite having the clinical features of ichthyosis and neurologic disease. This reflects the likelihood of considerable genetic heterogeneity in the neuro-ichthyotic syndromes and the existence of many unrecognized diseases.
Array Technology Available for Clinical Use for Diagnosis of Microdeletions / Microduplications
Mari Nelson, B.S., CLSp(CG/MB), Diane Pickering, M.S., CLSp(CG), & Warren Sanger, Ph.D.

Cytogenetic and molecular cytogenetic studies play an important role in the study of mental retardation since many conditions are associated with small chromosome deletions and duplications that are identified by G-banding and/or FISH studies. However, many chromosome abnormalities are submicroscopic and FISH studies are increasingly costly and time-consuming due to a growing number of “critical” chromosome regions to examine. Two comparative genomic hybridization (CGH) methodologies have been recently compared and validated for clinical use, by the Human Genetics Laboratory, for detection of submicroscopic cytogenetic deletions and duplications. One of these techniques, high resolution CGH is a molecular cytogenetic technique that utilizes two-color fluorescence in situ hybridization (FISH) and allows for a global overview of chromosomal losses and gains throughout the whole genome. This technique allows the detection of deletions as small as 3Mbp. Another technique, the GenoSensor 300 Microarray, is another CGH methodology which identifies gains or losses of approximately 287 genetic sequences known to be associated with clinical abnormalities, including all subtelomere regions. These technologies have been compared and validated and are ready for clinical use for identification of subtelomeric deletions, duplications, as well as interstitial chromosomal deletions and duplications. It should be noted that these two CGH assays only detect copy number changes and cannot detect structural rearrangements (inversions or balanced translocations) unless copy number changes have also occurred. The cost for this diagnostic approach is on the order of $1600 and the specimen requirements are peripheral blood in an EDTA tube or any tissue from which DNA can be extracted. Any questions regarding these techniques can be addressed by calling our laboratory at (402) 559-5070.

VIP (Very Important Personnel)
Melonie Welsh, M.S.

The Human Genetics Laboratory has hired 4 new Cytogenetic Technologists: Susan Brusnahan, MT(ASCP); Thomas Tucker, M.S., Abigail Wood, B.A., and Donna Pierson, B.S.. Kelli Novak, MT (ASCP), CLSp(CG) has returned after a 7 year absence. Sara Knavel, M.S. has joined our team as a Genetic Counselor. Sara provides service to both prenatal and general genetics patients. The highly trained staff includes 50 laboratory technologists, 5 clerical staff, a Lab Director, and 2 Associate Lab Directors. The clinical staff includes 6 Clinical Geneticists, 6 Genetic Counselors and 4 clerical staff.

Why pay money to have your family tree traced? Go into politics and your opponent will do it for you.

Mark Twain

<table>
<thead>
<tr>
<th>Specimen Type</th>
<th>Minimum</th>
<th>Mean</th>
<th>Specimen Type</th>
<th>Minimum</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amniotic fluid - cytogenetics</td>
<td>6</td>
<td>8</td>
<td>Blood (newborns)</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Amniotic fluid - aneuploid screen</td>
<td>1</td>
<td>2</td>
<td>Blood (non-stat)</td>
<td>3</td>
<td>14</td>
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<tr>
<td>Quad Fetal Risk Assessment</td>
<td>3</td>
<td>3</td>
<td>Blood (cancer)</td>
<td>2</td>
<td>5</td>
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<tr>
<td>Products of conception</td>
<td>10</td>
<td>15</td>
<td>Bone marrow</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Skin Biopsy</td>
<td>14</td>
<td>24</td>
<td></td>
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<td></td>
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</tbody>
</table>
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 (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