

MEDICAL GENETICS BIOCHEMICAL AND MOLECULAR LABORATORY ROTATION

Overview: The Medical Genetics Biochemical and Molecular Laboratory Rotation (MGLR) is a required rotation for the Medical Genetics Residents/Fellows (hereafter referred to as the MGF). The MGLR is a one month rotation that occurs in the Biochemical and DNA Diagnostic Laboratories of the Baylor College of Medicine (BCM) with a two-week block in the Biochemical Lab and a two-week block in the DNA Diagnostic (Molecular) Lab. The MGF will be supervised by Dr. William E. O'Brien while on the Biochemical portion of the rotation and by Dr. Benjamin B. Roa while on the Molecular portion of the rotation. The MGF will observe laboratory methodologies for diagnosis of enzyme deficiencies as well as other single gene disorders. The BCM Biochemical Laboratory offers a full range of testing for enzyme deficiencies including amino acid analysis, organic acid analysis and multiple assays for specific enzyme deficiencies. The BCM Molecular Laboratory likewise offers a wide range of testing for single gene disorders utilizing multiple molecular techniques including PCR, ASO hybridization, pyrosequencing, DHPLC, Southern analysis, methylation-specific Southern analysis, DNA sequencing, linkage analysis, PAGE, and agarose gel electrophoresis. Please see Section 7. Laboratory Data, B. Biochemical Genetics and C. Molecular Genetics for a listing of the tests performed in each lab respectively.

Biochemical Genetics Lab (2 weeks) Director: William E. O'Brien, Ph.D.

The MGF will observe techniques used in the biochemical genetics lab including amino acid analysis using HPLC (high-pressure liquid chromatography), urinary organic acid screening utilizing Gas chromatography/Mass spectrometry (GC/MS), and acylcarnitine profiling utilizing Tandem mass spectrometry (MS/MS). In addition, the laboratory conducts approximately 30 different enzyme assays that use fluorimetric, spectrophotometric, and radioisotopic determinations.

The MGF will observe how samples are received in the laboratory and prepared for analysis.

The MGF will observe the following representative tests from start to finish (including reporting the results):

Amino Acid Analysis – Amino acid analysis is the most utilized test in the screening of patients for metabolic disorders. The procedure utilizes HPLC to separate the amino acids and spectrophotometry to quantitate the results. The MGF will participate in the interpretation of results for this test with the laboratory director.

Urinary Organic Acid Screening – The screening for organic acidurias is also a major screening test for inborn errors of metabolism. This procedure uses the Gas Chromatograph/Mass Spectrometer and is an ideal introduction to the use of mass spectrometry in the diagnostic laboratory. The MGF will participate in the analysis of data with the laboratory director. The laboratory director will describe the methodology involved in the analysis and demonstrate the power of the mass spectrometer. The MGF will participate in the interpretation of results for this test with the laboratory director.

Plasma Acylcarnitine Analysis – This test is used for the diagnosis of inborn errors of metabolism involving fatty acid oxidation. The procedure utilizes the tandem mass spectrometer and provides an introduction to the use of tandem mass spectroscopy in newborn screening. (The laboratory does not do newborn screening.) The laboratory director will describe the methodology involved in the analysis and demonstrate the power of

the tandem mass spectrometer. The MGF will participate in the interpretation of results for this test with the laboratory director.

The MGF will also be exposed to many enzyme analyses that are used to diagnose inborn errors of metabolism.

The MGF will participate in conferences and telephone consultations with clinicians involved in patient care.

DNA Diagnostic Lab (2 weeks) Director: Benjamin B. Roa, Ph.D.

The MGF will be provided selected readings on the methodologies employed by the lab for study. The MGF will observe the process by which samples are received in the laboratory and how DNA samples are prepared for analysis.

The MGF will observe the following representative tests from start to finish (including reporting the results):

Fragile X syndrome testing –A combination of polymerase chain reaction (PCR analysis) and the traditional method of Southern Blotting are used. This test provides a good introduction to DNA testing for a whole class of neurogenetic diseases called the “triplet-repeat” syndromes. Fragile X also provides insights into disorder testing and interpretation of data for an X-linked disorder in males and females.

Hemochromatosis and Factor V Leiden testing – Molecular testing for known point mutations that are associated with increased risk or susceptibility for these relatively common genetic conditions. The frequently-occurring common mutations for these two disorders are analyzed using an automated mini-sequencing technology (Pyrosequencing). Data interpretation for these typically adult disorders addresses issues of penetrance, genetic predisposition and interaction of genetics and environment in disease.

Mutation scanning and/or DNA sequence analysis for multiple diseases – The DNA lab performs mutation scanning by DHPLC analysis and/or DNA sequencing for inherited colorectal cancer syndromes that include FAP and HNPCC, and neurogenetic diseases such as Rett syndrome and Angelman syndrome (for cases wherein the common AS mutations have been ruled out by normal DNA methylation studies). The MGF will observe the techniques of denaturing high-pressure liquid chromatography (DHPLC) and automated capillary DNA sequence analysis. Participation in data review and writing reports for these tests will help the MGF to understand how to interpret various types of nucleotide changes uncovered by DNA sequencing (nonsense mutations, frameshift mutations, missense mutations, splice-site mutations, benign polymorphisms, translationally silent substitutions, and sequence variants of unknown clinical significance, etc). Participation in report generation for these tests will provide insights regarding how to resolve ambiguous/unusual results by analysis of the parents or appropriate family members, and clinical correlation.

Conferences:

Biochemical Sign-out Conference is held every Tuesday from 11-12 at the BCM main campus. MGFs will attend both weeks while on the Biochemical portion of the Lab Rotation. MGFs will be encouraged to attend every week while on at least one of their two-month Advanced Clinical Medical Genetics Rotations during the second year of the Program.

Molecular Sign-Out Conferences are held for the following conditions: Duchenne/Becker muscular dystrophy, Triplet repeat disorders which include Fragile X syndrome, Colorectal

cancer syndromes, and other conditions as needed. Molecular Sign-out Rounds are held on site at the Molecular laboratory, and will be attended by the MGFs while on the two-week Molecular Rotation. In addition, the MGFs can attend Genetics Rounds which are held at the main Baylor campus on Fridays at noon, and DNA Diagnostic rounds which are held at the Medical Genetic Lab site once a month.

Legend for Learning Activities		
AR - Attending Rounds	M/DO - Modeling/Direct Observation	E/C—Ethics/Communication Conferences
FS – Faculty Supervision	ASR - Assigned Reading	JC - Journal Club
CSOC-Case Sign-Out Conference	WH - Written Homework	RC - Research Conference

Legend for Evaluation Methods for Residents	
AE - Attending Evaluation	DO - Direct Observation
DSP- Directly Supervised Procedures	RWH - Review of Written Homework
CR - Chart Review	CSR - Chart Stimulated Review
360° - Global Evaluation	

Principal Educational Goals and Objectives by Relevant Competency

The principal educational goals for residents on this rotation are indicated for the relevant ACGME competencies. The tables below each goal list the corresponding educational objectives, the relevant learning activities, and the evaluation methods for each objective. The educational goals and objectives are applicable to Medical Genetics Residents/Fellows. The expected competency level demonstrated by the residents should reflect their respective level of experience.

Competency 1 – Patient Care. Provide clinical care in the area of Medical Genetics to patients/families who are either affected or potentially affected by a condition that has a genetic component.

GOAL: Observe laboratory techniques utilized in biochemical genetic testing obtained on patients who are under assessment as possibly affected by a genetic disease.

	Principal Educational Objectives	Learning Activities	Evaluation Methods
1.	Observe the following laboratory techniques: HPLC (high-pressure liquid chromatography), gas chromatography/mass spectrometry (GC/MS), tandem mass spectrometry (MS/MS) and enzyme assays that use fluorimetric and spectrophometric determinations.	M/DO, FS	AE, DO

GOAL: Observe laboratory techniques utilized in molecular genetic testing obtained on patients who are under assessment as possibly affected by a genetic disease.

	Principal Educational Objectives	Learning Activities	Evaluation Methods
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1.	Observe testing for the following conditions: Fragile X syndrome, hemochromatosis, Factor V Leiden, Rett syndrome and Angelman syndrome. Testing methodologies that will be observed include: PCR and Southern blotting (Fragile X syndrome); an automated mini-sequencing technology (Pyrosequencing) [hemochromatosis and Factor V Leiden testing]; and DHPLC (Rett syndrome) and direct sequencing (Rett syndrome and Angelman syndrome).	M/DO, ASR, FS, CSOC	AE, DO
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Competency 2 - Medical Knowledge. Understanding the scope of established and evolving biomedical, clinical, epidemiological and social-behavioral knowledge needed by a Medical Geneticist; demonstrate the ability to acquire, critically interpret and apply this knowledge in patient care.

GOAL: Demonstrate knowledge regarding the results generated through testing in the Biochemical Genetics Laboratory.

	Principal Education Objectives	Learning Activities	Evaluation Methods
1.	Participate in interpretation of laboratory data by the Biochemical Laboratory Director to diagnose inborn errors of metabolism and manage metabolic disease.	M/DO, FS, CSOC	AE, DO, CR

GOAL: Demonstrate knowledge regarding the results generated through testing in the Molecular Genetics Laboratory.

	Principal Education Objectives	Learning Activities	Evaluation Methods
1.	Participate in interpreting and reporting of results for Fragile X testing demonstrating understanding of results for a typical triple repeat expansion disorder in both males and females.	M/DO, FS, CSOC, ASR, WH	AE, DO, CR, RWH
2.	Participate in interpreting and reporting testing for hemochromatosis and Factor V Leiden addressing the issues of penetrance, genetic predisposition, and interaction of genes and environment in disease.	M/DO, FS, CSOC, ASR, WH	AE, DO, CR, RWH
3.	Participate in interpreting and reporting results for Familial Adenomatous Polyposis (FAP) and Rett syndrome testing. Data interpretation followed by generation of a report in these cases will address how to interpret different nucleotide changes observed (nonsense mutations, frameshift mutations, missense mutations, splice-site mutations, benign polymorphisms, translationally silent substitutions, and sequence variants of unknown clinical significance). Further, the MGF needs to demonstrate decision-making ability regarding the “next step” in resolving ambiguous/novel/unusual results.	M/DO, FS, CSOC, ASR, WH	AE, DO, CR, RWH

Competency 3 – Interpersonal and Communications Skills. Demonstrate interpersonal and communication skills that result in information exchange and partnering with patients, their families and professional associates.

GOAL: Participate in provision of results from the Biochemical and Molecular Genetic Laboratories to referring genetic counselors/physicians or other appropriate professionals.

	Principal Educational Objectives	Learning Activities	Evaluation Methods
1.	Participate in/provide results of biochemical and molecular genetic testing to genetic counselors/physicians/other appropriate professionals.	WH, FS, M/DO	AE, DO
2.	Communicate effectively with genetic counselors, physicians, other health professionals, and health related agencies to create and sustain information exchange and team work for patient care.	FS, M/DO	AE, DO

Competency 4 – Practice-based Learning and Improvement. Demonstrate knowledge, skills and attitudes needed for continuous self-assessment, using scientific methods and evidence to investigate, evaluate, and improve one’s patient care practice.

	Principal Educational Objectives	Learning Activities	Evaluation Methods
1.	Develop strategies to learn about future advances in the understanding of the biochemical and molecular bases of genetic disease, in order to incorporate into one’s practice improved screening, identification, counseling and management of these disorders.	ASR, M/DO, CSOC	DO, AE
2.	Identify personal learning needs, systematically organize relevant information resources for future reference, and plan for continuing data acquisition if appropriate.	ASR, M/DO	DO, AE,

Competency 5 – Professionalism. Demonstrate a commitment to carrying out professional responsibilities, adherence to ethical principles, and sensitivity to diversity.

	Principal Educational Objectives	Learning Activities	Evaluation Methods
1.	Discuss the ethical, legal, financial and social issues involved in genetic testing of patients/families, especially testing of children for disease status, and providing medical care for patients with known fatal disorders.	CSOC, E/C, M/DO	AE, DO
2.	Demonstrate personal accountability to the well being of all patients, even when other physicians are primarily responsible for their care, for example, by interpreting laboratory results and following with referring genetic counselors/physicians as appropriate.	M/DO, FS,	AE, DO
3.	Demonstrate a commitment to carrying out professional responsibilities, adherence to ethical and legal principles, and sensitivity to diversity while providing care to patients/families with genetic disease.	M/DO, FS	AE, DO

Competency 6 - Systems-Based Practice. Understand how to practice quality health care and advocate for patients within the context of the health care system.

	Principal Educational Objectives	Learning Activities	Evaluation Methods
1.	Identify written and internet resources to aid in counseling patients/families with biochemical and molecular genetic diseases including availability of research studies in which the patients/families might wish to participate.	ASR, WH, CSOC	AE, DO
2.	Demonstrate sensitivity to the costs of clinical care in Medical Genetics and take steps to minimize costs without compromising	M/DO, FS	AE, DO

	quality.		
3.	Recognize the limits of one's knowledge and expertise and take steps to avoid laboratory errors.	M/DO, FS	AE, DO
4.	Understand key aspects of health care systems as they apply to care of patients and their families, including cost control, billing and reimbursement.	M/DO, FS	AE, DO
5.	Recognize and advocate for families who need assistance to deal with systems complexities, such as lack of insurance.	M/DO, FS	AE. DO