Chromosome Breakage Disorders Panel by next-generation sequencing (NGS)

Genes Tested

ATM	*BLM*	*LIG4*	*NBN*	*NHEJ1*

Description:

Chromosome breakage disorders are a group of related diseases which are characterized by spontaneous chromosome breakage, immunodeficiency and predisposition to malignancy.

Ataxia-Telangiectasia (A-T) is a rare, neurodegenerative disorder, with an estimated incidence of 1 in 40,000-100,000 births. A-T is caused by mutations in the *ATM* gene and is characterized by immunodeficiency, progressive cerebellar ataxia, telangiectasia of the skin and eyes, and susceptibility to cancer. Approximately one-third of A-T patients develop cancer, typically leukemia or lymphoma in childhood, while approximately one-half of patients have immunodeficiencies, usually characterized by deficiency of naïve T cells and decreased or absent IgA, IgE and IgG2. Malignancy, pneumonia and chronic lung disease, as a result of immunodeficiency, contribute to early deaths.

Bloom syndrome is caused by mutations in the *BLM* gene. Our cytogenetics laboratory offers diagnostic testing via sister chromatid exchange (SCE) analysis, rates of which are elevated in patients with Bloom syndrome. Bloom syndrome is characterized by immune deficiency and predisposition to cancer, severe pre- and postnatal growth deficiency, sparseness of subcutaneous fat tissue, an erythematous, sun-sensitive "butterfly" lesion on the face and impaired fertility. Serum concentrations of immunoglobulins are typically low. Common health complications include life-threatening infections and chronic obstructive lung disease, gastroesophageal reflux, and type 2 diabetes. Patients with Bloom syndrome have a dramatically increased risk of cancer, primarily leukemias and lymphomas in childhood and solid tumors in adulthood, occurring at earlier than normal ages. The most common cancers detected in adults include tumors of the lower enteric tract, integument, esophageal/upper respiratory tract and genital/urinary tract.

Nijmegen breakage syndrome, LIG4 syndrome and **NHEJ1 deficiency**, caused by biallelic mutations in *NBN*, *LIG4* and *NHEJ1* respectively, are similar disorders characterized by microcephaly, growth retardation, combined immune deficiency and sensitivity to ionizing radiation. All are associated with much elevated risks of malignancy in affected individuals.

Genetics:

Each of these rare disorders is inherited as an autosomal recessive condition. It is not known if the risk of malignancy is increased above the general population risk in heterozygous carriers of these disorders.

Indications:

Confirmation of diagnosis in individuals with the following symptoms:

- Unexplained pre- and postnatal growth deficiency, failure to thrive and small stature in association with immune deficiency or cancer
- Characteristic "butterfly" erythematous facial lesion
- Progressive cerebellar ataxia in young children

Cincinnati Children's®

Human Genetics

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Indications continued:

- Recurrent infections or immunodeficiency in association with microcephaly
- History of leukemia, lymphoma or solid tumor at an earlier than expected age, particularly in association with other features of chromosome breakage disorder
- Increased sister chromatid exchange as detected cytogenetically, chromosomal instability or increased cellular sensitivity to ionizing radiation
- Unexpected toxicity to chemotherapy or radiation therapy
- Borderline increased chromosome breakage with DEB exposure.

Specimen: At least 5 mLs whole blood in a lavender top (EDTA) tube. Label tube with patient's name, birth date, and date of collection.

Testing Methodology: This test is performed by enrichment of the exons, flanking intronic and un-translated regions (5' and 3') of the genes specified above using microdroplet PCR technology followed by next-generation sequencing with > 40 fold coverage at every target base. All pathogenic and novel variants, as well as variants of unknown (indeterminate) significance, as determined bioinformatically, are confirmed by Sanger sequencing.

Sensitivity:

Clinical Utility:

- *ATM* is the only gene associated with ataxia-telangiectasia. Over 99% of individuals with classic ataxia-telangiectasia have mutations in *ATM*.
- *BLM* is the only gene associated with Bloom syndrome. Approximately 93% of individuals with clinical Bloom syndrome have mutations identified in *BLM*.

Clinical Utility continued:

- *NBN* is the only gene associated with NBS. Approximately 50% of individuals with clinical NBS-like symptoms and radio sensitivity have identified mutations. Mutations in *LIG4* and *NHEJ1* have been described in a few patients with similar findings.

Clinical Sensitivity: This testing methodology will detect 90% of mutations in *ATM*, 94% of mutations in *BLM* and over 99% of reported mutations in *NBN*. Large deletions and complex rearrangements have been reported in *NHEJ1* and will not be detected by this test. All mutations described in *LIG4* to date should be detected by this test.

Analytical Sensitivity: The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed.

Mutations in regulatory regions or other untranslated regions are not detected by this test. Large deletions involving entire single exons or multiple exons, large insertions and other complex genetic events have been reported in *ATM* and *BLM* and will not be identified using this test methodology. Rare primer site variants may lead to erroneous results.

Note: Single gene sequencing is available for all genes in the panel.

Turn-Around Time:

- Up to 12 weeks for NGS of the panel
- 4-12 weeks for analysis of any gene by Sanger sequencing

Cost: Please call 1-866-450-4198 for current pricing, insurance preauthorization or with any billing questions.

CPT Codes:

- Chromosome Breakage Disorders by NGS — 81408, 81479x4
- Single gene sequencing of *ATM* — 81408
- Single gene sequencing of *BLM, LIG4, NBN, NHEJ1* — 81479

Results: Results will be reported to the referring physician or health care provider as specified on the requisition form.

Shipping Instructions

Please enclose **test requisition** with sample. **All information must be completed before sample can be processed**. Place samples in Styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship to:

Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229

513-636-4474

References:

Cagdas, D., et al. (2012). Pediatr Transplant, 16(5), E167-171.

Chistiakov, D. A. (2010). Adv Exp Med Biol, 685, 175-185.

Chrzanowska, K. H. et al. (2012) Orphanet J Rare Dis, 7, 13.

Concannon, P. and Gatti, R. "Nijmegen Breakage Syndrome – GeneReviews." Updated 1 Mar 2011, http://www.ncbi.nlm.nih.gov/books/NBK1176/

Derheimer, F. A. and Kastan, M. B.. (2010) FEBS Lett, 584(17), 3675-81.

Dvorak, C. C., et al. (2010). Immunol Allergy Clin North Am, 30(1), 125-142.

Exley, A. R. et al. (2011) Clin Immunol, 140(1), 26-36.

Gatti, R. "Ataxia-Telangiectasia – GeneReviews." Updated 11 Mar 2010. http://www.ncbi.nlm.nih.gov/books/NBK26468/

German, J. et al. (2007) Hum Mutat, 28(8), 743-53.

Kaneko, H. and Kondo, N. (2004) Expert Rev Mol Diagn, 4(3), 393-401.

Masuda, Y., et al. (2012). Int J Hematol, 95(3), 239-245.

Sanz, M, and German, J. "Bloom's Syndrome-GeneReviews." Updated 24 Aug 2010. http://www.ncbi.nlm.nih.gov/books/NBK1398/

Staples, E. R. et al. (2008) Clin Exp Immunol, 153(2), 214-20.

Tewhey, R, et al. (2009). Nat Biotechnol, 27(11), 1025-1031.

Thusberg, J, et al. (2011). Hum Mutat, 32(4), 358-368.

Turul, T., et al. (2011). J Investig Allergol Clin Immunol, 21(4), 313-316.

van der Burg, M., et al. (2006). J Clin Invest, 116(1), 137-145.