Intramural papers of the month

By Kimberly Cannady, Deacqunita Diggs, Simone Otto, and Bailey Schug

Allergy prevalence the same in U.S. no matter where you live

Scientists from NIEHS have shown the prevalence of allergies is the same, regardless of where you live in the U.S., except in children 5 years and younger. The researchers analyzed blood serum data from approximately 10,000 Americans in the National Health and Nutrition Examination Survey (NHANES) 2005-2006. The findings constitute the largest and most comprehensive nationwide study to examine allergy prevalence from early childhood to old age.
The survey analyzed serum for nine different antibodies in children aged 1-5, and 19 different antibodies in participants 6 years and older. While the overall prevalence of allergies did not differ between regions, except in early childhood, allergies to specific allergens and allergen types varied regionally. Allergies also tended to aggregate in clusters of allergens that were similar.

Males, non-Hispanic blacks, and those who avoided pets had an increased chance of having allergies, among those 6 years and older. Children aged 1-5 from the southern U.S. displayed a higher prevalence to allergies than their peers living elsewhere. Although socioeconomic status (SES) did not predict allergies, allergies to dogs and cats were more common in higher SES groups, whereas allergies to cockroaches and shrimp were more common in lower SES groups. **(BS)**

Citation: Salo PM, Arbes SJ Jr, Jaramillo R, Calatroni A, Weir CH, Sever ML, Hoppin JA, Rose KM, Liu AH, Gergen PJ, Mitchell HE, Zeldin DC.
(http://www.ncbi.nlm.nih.gov/pubmed/24522093)
2014. Prevalence of allergic sensitization in the United States: Results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol; doi:10.1016/j.jaci.2013.12.1071 [Online 9 February 2014]. [Story]

DNA polymerase mu has a novel mechanism for binding DNA

NIEHS researchers have discovered a novel mechanism by which a DNA polymerase can bind and repair DNA. Polymerase mu is a template-dependent polymerase, like Pol beta and Pol lambda. Previous work investigating Pol beta and Pol lambda emphasized conformational changes and kinetic checkpoints considered crucial for correct DNA repair. Pol mu preserves sequence during a type of double-stranded DNA repair, known as V(D)J recombination, used to make the immunoglobulin light chains necessary for B cells. It is also important in development and DNA repair.

To determine the structure of Pol mu, scientists created a truncated polymerase and characterized its structure during its catalytic cycle. They found minimal conformational change, other than repositioning of loop 1. The rigidity of the overall polymerase, combined with the flexibility of loop 1, allows Pol mu to bind and stabilize the DNA ends of double strand breaks with discontinuous structure. Thus, Pol mu can interact with a selection of DNA substrates with varying structures. To verify that loop 1 is important in substrate selection, scientists mutated specific residues. The resultant loss of activity on specific types of substrates supports the importance of loop 1. **(SO)**

Citation: Moon AF, Pryor JM, Ramsden DA, Kunkel TA, Bebenek K, Pedersen LC.
(http://www.ncbi.nlm.nih.gov/pubmed/24487959)
2014. Sustained active site rigidity during synthesis by human DNA polymerase mu. Nat Struct Mol Biol 21(3):253-260.

MBD3 studies suggest NuRD complex regulates chromatin structure

NIEHS scientists and their collaborators determined that Mi-2/nucleosome remodeling and histone deacetylase (NuRD) complex regulates chromatin structure, by changing the location or chemical properties of the nucleosome, a building block of chromatin. The researchers performed localization studies to map methyl-CpG binding domain protein 3 (MBD3), a component of NuRD complex, within the genome. This work highlights the importance of understanding NuRD function, since mutations within the complex frequently occur in cancer.

The researchers used DNA adenine methyltransferase identification (DamID) and chromatin immunoprecipitation, coupled with massive parallel sequencing (ChIP-seq), to map MBD3 localization in two breast cancer cell lines. Accessing histone

modification data from the ENCODE project, the authors defined the genomic chromatin features bound by MBD3. They observed cell-type specific MBD3 localization patterns at the promoters, gene bodies, and enhancers of active genes. Moreover, they discovered that depletion of MBD3 results in the decrease of nucleosome occupancy at promoter and enhancer regions.

Overall, these studies suggest a role for MBD3, and thus the NuRD complex, in regulating chromatin structure. The researchers propose that this data provides a good starting point to begin addressing the mechanisms through which NuRD modulates the epigenetic landscape. **(KC)**

Citation: Shimbo T, Du Y, Grimm SA Dhasarathy A, Mav D, Shah RR, Shi H, Wade PA.
(http://www.ncbi.nlm.nih.gov/pubmed/24385926)
2014. MBD3 localizes at promoters, gene bodies and enhances of active genes. PLoS Genet 9(12):e1004028.

MicroRNA expression levels differ in breast cancer patients

According to NIEHS researchers and their collaborators, the expression patterns of serum microRNAs (miRNAs), small, non-coding, single-stranded RNAs, differed between women who later developed cancer versus those who remained cancer free. The scientists examined blood samples obtained from 410 participants in the Sister Study, a nationwide cohort of more than 50,000 women whose sister had breast cancer. It is the first study to use specimens collected before the onset of disease, known as a prospective collection.

The study examined blood from 205 women who subsequently developed cancer, and 205 who did not. Using Affymetrix arrays, the authors detected 414 miRNAs and determined that 21 of 414 miRNAs were significantly different in women who developed breast cancer. Three miRNAs from this group, miR-18a, miR-181a, and miR-222, had the highest expression in a small, independent replication study. In addition, there was some evidence that circulating miRNAs were correlated with the type and severity of the tumor that subsequently developed in the women.

The authors noted that while it may be possible to use miRNAs as an early detection tool, further studies that utilize a larger sample size, as well as specimens from women without a family history of breast cancer, are needed. **(DD)**

Citation: Godfrey AC, Xu Z, Weinberg CR, Getts RC, Wade PA, DeRoo LA, Sandler DP, Taylor JA.
(http://www.ncbi.nlm.nih.gov/pubmed/23705859)
2013. Serum microRNA expression as an early marker for breast cancer risk in prospectively collected samples from the Sister Study cohort. Breast Cancer Res 15(3):R42.

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