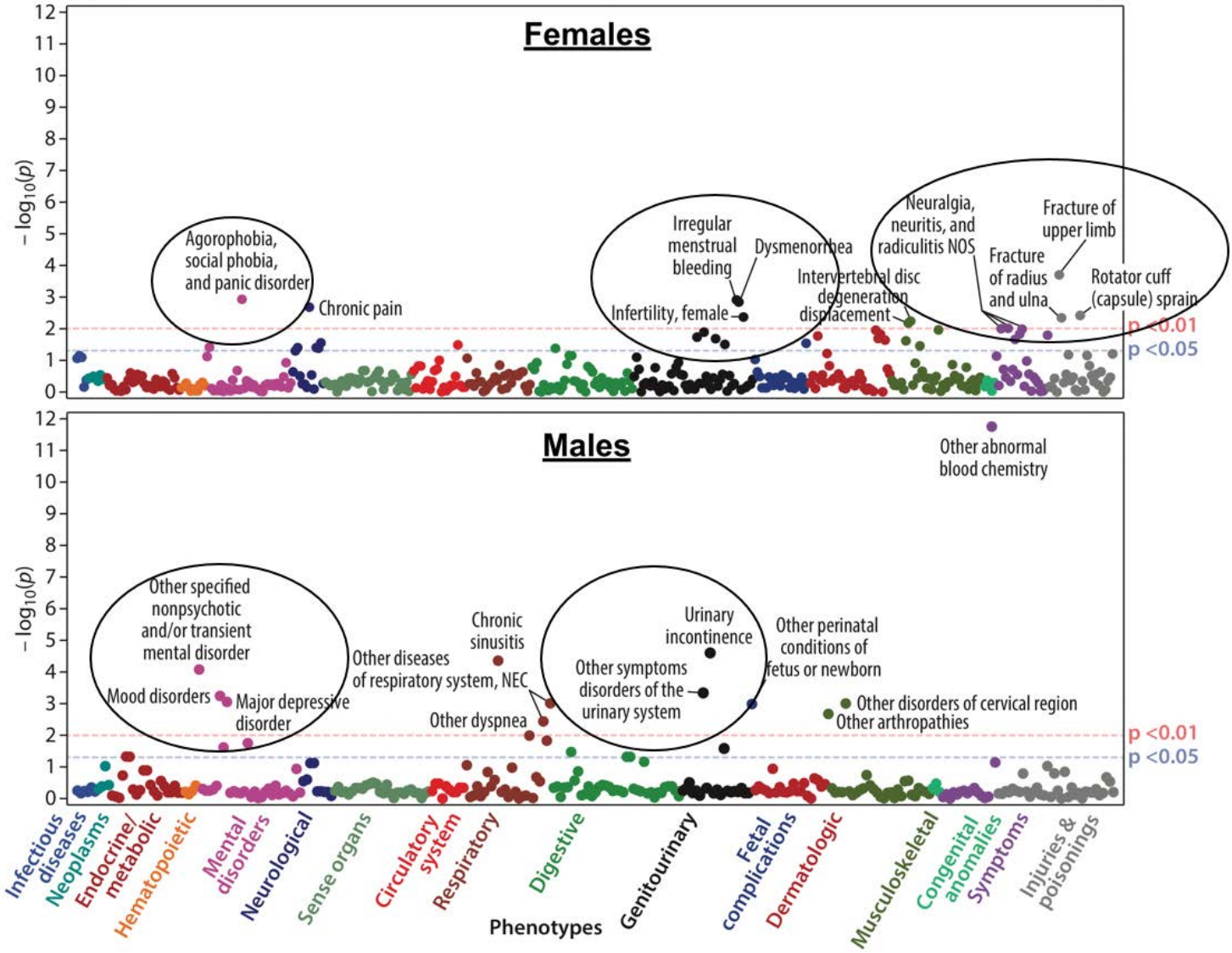

Title: Population screening and double-blind phenotyping identifies higher burden of disease in *FMR1* premutation carriers compared to the normal population.

Legend: Manhattan plots of unadjusted $-\log_{10}$ (P-values) for clinical phenotypes observed before age 40 in *FMR1* premutation carriers compared to the normal controls. Each point shows one phenotype. Only associations with p-value<0.01 are annotated. Three phenotypic categories were strongly related to premutation status in females: reproductive problems, injuries, and anxiety. Indicators of Fragile X primary ovarian insufficiency (FXPOI) including infertility, menstrual related symptoms, and dysmenorrhea were observed in these individuals. Male premutation carriers experienced elevated rate of mental health problems, respiratory conditions, genitourinary disorders, and musculoskeletal diseases**.** Early possible signs of Fragile X associated tremor/ataxia syndrome (FXTAS) were observed in male premutation carriers including mood disorder, incontinence, and arthropathies.

Citation: Movaghar, A., Page, D., Brilliant, M., Baker, M. W., Greenberg, J., Hong, J., Dawalt, L. S., Saha, K., Mailick, M., 2018. Gatlinburg Conference Poster Submission PS-48.

Abstract: The *FMR1* premutation affects millions of people around the globe. Despite the high prevalence, the potential impact of this genetic variant on human health has not been fully explored. Here, we created the first population-based *FMR1*-informed biobank to discover the pattern of health characteristics in premutation carriers. We have used a novel and unbiased approach to examine the electronic health records (EHRs) from 98 premutation carriers (72 females, 26 males), and 1,001 (507 females, 494 males) age-matched controls with CGGs in the normal

range (i.e., 24–40 CGG repeats). Using a supervised machine learning method, we were able to successfully predict the participants' *FMR1* premutation status. Our extensive computational phenotyping showed that premutation carriers suffer from more health difficulties over their life span compared to the normal population. Phenome-Wide Association Study (PheWAS) methodology, was utilized to further examine the phenotypic association of clinical diagnoses and *FMR1* premutation. We identified 37 significant associations in females categorized in 3 significant groups: reproductive problems, injuries, and anxiety. 22 significant associations were identified in male participants including categories such as mental disorders, respiratory conditions, genitourinary disorders, and musculoskeletal diseases, all of which were elevated in premutation carriers. Comprehensive understanding of these clinical risks is critical for premutation carriers, their families and clinicians and could be potentially used in developing personalized health plans and preventive care.

About the Lab: The Lifespan Family Research Program conducts research about families who have a member with a disability, with a special emphasis on how these families change over the lifespan. Currently, our program of research encompasses longitudinal and population-based studies of autism and fragile x syndrome, and we develop evidence-based interventions for affected families. One recent project includes investigation of genotype-phenotype correlations between the full range of CGG repeats in the *FMR1* gene and outcomes such as cognition and physical and mental health.

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