THE CHINESE UNIVERSITY OF HONG KONG
FACULTY OF MEDICINE
SCHOOL OF BIOMEDICAL SCIENCES

SBS PI Seminar Series 2023-2024

Prof. GU Shen Linda

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will present a seminar entitled

"Monoallelic variation in DHX9 *underlies neurodevelopment disorders and beyond"*

DExD/H-box RNA helicases (DDX/DHX) are encoded by a large paralogous gene family; in a subset of these human helicase genes, pathogenic variation causes neurodevelopmental disorder (NDD) traits and cancer. *DHX9* encodes a BRCA1-interacting nuclear helicase regulating transcription, R-loops, and homologous recombination and exhibits the highest mutational constraint of all DDX/DHX paralogs but remains unassociated with disease traits. Using exome sequencing and family-based rare-variant analyses, we identified 20 individuals with *de novo*, ultra-rare, heterozygous missense or loss-of-function (LoF) *DHX9* variant alleles. Phenotypes ranged from NDDs to the distal symmetric polyneuropathy axonal Charcot-Marie-Tooth disease. Quantitative Human Phenotype Ontology analysis demonstrated genotype-phenotype correlations with LoF variants causing mild NDD phenotypes and nuclear localization signal missense variants causing severe NDD. We investigated *DHX9* variant-associated cellular phenotypes in human cell lines. *Dhx9*$^{-/-}$ mice exhibited hypoactivity in novel environments, tremor, and sensorineural hearing loss. Collectively, these results establish *DHX9* as a critical regulator of mammalian neurodevelopment and neuronal homeostasis.

21 March 2024, Thursday, 4:00 pm– 5:00 pm

Room G02, Lo Kwee-Seong Integrated Biomedical Sciences Building,
Area 39, The Chinese University of Hong Kong