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Symposium A3 (Medial Genetics): Pathway Disorder (October 6, 10:45-12:15)
Title: Rasopathies – Noonan syndrome and related disorders
Speaker: Yoichi Matsubara (National Center for Child Health and Development, Japan)

Abstract:
Rasopathies or RAS/MAPK syndromes are a group of phenotypically related syndromes caused by germline mutations of genes encoding components of the RAS/MAPK signaling pathway, which controls cell proliferation, differentiation and survival. These disorders includeNoonan syndrome, Noonan syndrome with multiple lentigines (formerly called LEOPARD syndrome), Costello syndrome, cardiofaciocutaneous (CFC) syndrome, Noonan-like syndrome, neurofibromatosis type I, Legius syndrome, hereditary gingival fibromatosis and capillary malformation-arteriovenous malformation. Although each Rasopathy has a unique phenotype, these syndromes have many overlapping characteristics, including craniofacial dysmorphology, cardiovascular abnormalities, musculoskeletal abnormalities, cutaneous lesions, neurocognitive impairment and increased risk of tumor. To date various disease-causing genes have been identified, such as *PTPN11, SOS1, SOS2, RAF1, NRAS, RIT1, RRAS, RASA2, LZTR1, A2ML1, KRAS, BRAF, HRAS, MAP2K1/2, SHOC2, CBL, NF1, SPRED1,* and *RASA1*. The identification of the causative genes that underlie the Rasopathies has facilitated molecular diagnosis of these disorders, enabled the evaluation of genotype–phenotype relationships and aided in the development of possible therapeutic approaches. Inhibitors of the RAS/MAPK signaling cascade may offer a means of therapeutically treating disorders that involve dysregulation of the RAS/MAPK pathway. Indeed, MEK inhibitors have been shown to ameliorate the phenotype of knock-in mouse models for NS and CFC syndrome, suggesting that the phenotypes that are produced by Rasopathies can be ameliorated by manipulating RAS/MAPK activity.