Genomics Links Autophagy with Neurocognitive Impairment in HIV-Infected Children

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OBJECTIVE
To identify host genetic variants associated with NCI in PHIV children (2 months – 18 years).

METHODS
• One Discovery Cohort (DC) and two Validation Cohorts (VC) of PHIV children were assessed.
• Discovery Cohort: Participants from PACTG 152 and PACTG 350 studies that predated effective cART; neurocognitive assessments were performed prior to the initiation of any ARVs (NEJM 1997;336:1704; J Pediatr 1998;133:500; Pediatr 1999:104:32).
• Validation Cohorts:
  • VC1: Pediatric HIV/AIDS Cohort Study (PHACS) Master Protocol (AMP); a contemporary cohort of PHIV children enrolled between the ages of 7 and 18 yrs and followed longitudinally.
  • VC2: PACTG 338 and PACTG 377; Enrolled HIV infected children between 4 mo (P377) or 24 mo and followed longitudinally.
• Genomics: Genome wide exome sequencing in a Discovery Cohort of 217 HIV-infected children and Validation Cohorts identified yielding 29 SNPs in 24 genes.
• Functional Studies: Gene silencing of CCRL2, FAM134B and YWHAH (14-3-3) in human monocyte derived microglial cells (MG) treated with HIV ssRNA alter inflammation through the modulation of autophagy. These findings suggest that genetic variants that alter the inflammatory response of microglial cells to HIV ssRNA alter inflammation mediated by alterations in autophagy.

RESULTS
• 29 SNPs identified in 24 genes in Discovery Cohort.
• 3 SNPs were re-evaluated in VC2.
• Consistent with the effects on NCI, silencing experiments demonstrate that loss of function FAM134B and YWHAH results in increased inflammation while loss of function of CCRL2 results in decreased inflammation.

CONCLUSIONS
Gene silencing of CCRL2, FAM134B and YWHAH are all potentially involved in the modulation of the inflammatory response as measured by Interleukin-1β (IL-1β).

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