

# PACS1 Related Syndrome

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The Schuurs&#8722;Hoeijmakers syndrome (SHMS) or PACS1 Neurodevelopment Disorder (PACS1-NDD) is a rare autosomal dominant disease caused by mutations in the PACS1 gene. To date, only 87 patients have been reported and, surprisingly, most of them carry the same variant (c.607C>T; p.R203W). The most relevant clinical features of the syndrome include neurodevelopment delay, seizures or a recognizable facial phenotype. Moreover, some of these characteristics overlap with other syndromes, such as the PACS2 or Wdr37 syndromes. The encoded protein phosphofurin acid cluster sorting 1 (PACS-1) is able to bind to different client proteins and direct them to their subcellular final locations. Therefore, although its main function is protein trafficking, it could perform other roles related to its client proteins. In patients with PACS1-NDD, a gain-of-function or a dominant negative mechanism for the mutated protein has been suggested. This, together with the fact that most of the patients carry the same genetic variant, makes it a good candidate for novel therapeutic approaches directed to decreasing the toxic effect of the mutated protein. Some of these strategies include the use of antisense oligonucleotides (ASOs) or targeting of its client proteins.