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Genes underlying delayed puberty

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1 Genes Underlying Delayed Puberty

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21 Abstract

22 The genetic control of pubertal timing has been a field of active investigation for  
23 the last decade, but remains a fascinating and mysterious conundrum. Self-  
24 limited delayed puberty (DP), also known as constitutional delay of growth and  
25 puberty, represents the extreme end of normal pubertal timing, and is the  
26 commonest cause of DP in both boys and girls. Familial self-limited DP has a  
27 clear genetic basis. It is a highly heritable condition, which often segregates in an  
28 autosomal dominant pattern (with or without complete penetrance) in the  
29 majority of families. However, the underlying neuroendocrine pathophysiology  
30 and genetic regulation has been largely unknown. Very recently novel gene  
31 discoveries from next generation sequencing studies have provided insights into  
32 the genetic mutations that lead to familial DP. Further understanding has come  
33 from sequencing genes known to cause GnRH deficiency, next generation  
34 sequencing studies in patients with early puberty, and from large-scale genome  
35 wide association studies in the general population. Results of these studies  
36 suggest that the genetic basis of DP is likely to be highly heterogeneous.

37 Abnormalities of GnRH neuronal development, function, and its downstream  
38 pathways, metabolic and energy homeostatic derangements, and transcriptional  
39 regulation of the hypothalamic-pituitary-gonadal axis may all lead to DP. This  
40 variety of different pathogenic mechanisms affecting the release of the puberty  
41 'brake' may take place in several age windows between fetal life and puberty.

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