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Review

Genetic determinants of pubertal timing in the general population

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ABSTRACT

Puberty is an important developmental stage during which reproductive capacity is attained. The timing of puberty varies greatly among healthy individuals in the general population and is influenced by both genetic and environmental factors. Although genetic variation is known to influence the normal spectrum of pubertal timing, the specific genes involved remain largely unknown. Genetic analyses have identified a number of genes responsible for rare disorders of pubertal timing such as hypogonadotropic hypogonadism and Kallmann syndrome. Recently, the first loci with common variation reproducibly associated with population variation in the timing of puberty were identified at 6q21 in or near *LIN28B* and at 9q31.2. However, these two loci explain only a small fraction of the genetic contribution to population variation in pubertal timing, suggesting the need to continue to consider other loci and other types of variants. Here we provide an update of the genes implicated in disorders of puberty, discuss genes and pathways that may be involved in the timing of normal puberty, and suggest additional avenues of investigation to identify genetic regulators of puberty in the general population.

Contents

1. Introduction

The timing of puberty varies greatly in the general population and is influenced by both genetic and environmental factors (reviewed by Parent et al., 2003; Gajdos et al., 2009; Hodges and Palmert, 2007; Palmert and Hirschhorn, 2003; Plant and Barker-Gibb, 2004; Towne et al., 2005). The high correlation of the onset

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of puberty seen within racial/ethnic groups, within families, and between monozygotic compared to dizygotic twins all provide evidence for genetic regulation of pubertal timing. Taken together, these data suggest that 50–80% of the variation in pubertal timing is determined by genetic factors (Parent et al., 2003; Hodges and Palmert, 2007; Palmert and Hirschhorn, 2003; Plant and Barker-Gibb, 2004; Towne et al., 2005; Fischbein, 1977; Sklad, 1977; Kaprio et al., 1995; van den Berg and Boomsma, 2007). Environmental and physiologic effects also influence the timing of puberty, and there is evidence supporting secular trends in the timing of puberty (Parent et al., 2003, 2005; Demerath et al., 2004; Euling et al., 2008). It is possible that gene by environment interactions play an important role in regulating the timing of puberty. However, despite changing environmental and secular influences, genetic background still plays a significant role in regulating the variation of pubertal timing within a population at any particular point in time. Thus, while acknowledging the importance of environmental factors, in this review we highlight the use of genetic methodologies to investigate the regulation of pubertal timing.

Much progress has been made in identifying genetic causes of disorders of puberty, such as hypogonadotropic hypogonadism (HH) and Kallmann syndrome (KS), but the specific genetic factors that regulate the variation in pubertal timing in the general population are just emerging. The identification of these genes has been difficult because pubertal timing is a complex genetic trait, where a direct, often one-to-one relationship between genotype and phenotype does not exist (Darvasi, 1998), likely due to multigenic influences and interactions between genetic variants and environmental exposures (Palmert and Boepple, 2001).

2. Insights from single gene disorders

Investigation of HH and KS has led to the identification of many genes that play critical roles in the development and regulation of the hypothalamic pituitary gonadal (HPG) axis (reviewed by Palmert and Hirschhorn, 2003; Bianco and Kaiser, 2009; Bhangoo and Jacobson-Dickman, 2009; Herbison, 2007; Kalantaridou and Chrousos, 2002; Silveira et al., 2002). For example, this work has defined roles for the genes that lead to HH (*GNRHR*, *GNRH1*, *GPR54*, *FGFR1*, *FGF8*, *PROK2*, *PROKR2*, *TAC3*, *TACR3*, and *CHD7*), to X-linked (*KAL1*) and autosomal (*FGFR1*, *PROK2*, *PROKR2*, *FGF8*, and *CHD7*) forms of KS, to obesity and HH (*LEP*, *LEPR*, and *PC1*), and to abnormal HPG development (*DAX1*, *SF-1*, *HESX-1*, *LHX3*, and *PROP-1*).

Genetic causes of other disorders of pubertal development, such as precocious puberty, have been previously reviewed (Herbison, 2007; Achermann et al., 2002). In this review, we focus on discussion of genes that are hypothesized to regulate pubertal timing at the hypothalamic level.

2.1. Normosmic hypogonadotropic hypogonadism

HH with normal olfaction has been primarily associated with mutations in the genes for the gonadotropin-releasing hormone receptor (*GNRHR)* and the G-protein coupled receptor 54 (*GPR54*), the G-protein coupled receptor for kisspeptins (the products of *KISS1*) (de Roux et al., 1997, 2003; Messager et al., 2005; Seminara et al., 2003; Shahab et al., 2005; Bedecarrats et al., 2003a,b; Wolczynski et al., 2003; Karges et al., 2003). Estimates of the frequency of *GNRHR* mutations in normosmic HH range from 3.5 to 10.4% (Bhagavath et al., 2005; Beranova et al., 2001). Recently, mutations in *GNRH1* were also identified in patients with normosmic HH (Chan et al., 2009; Bouligand et al., 2009). A case of constitutional delay of growth and puberty (CDGP) was reportedly associated with a homozygous partial loss of function mutation in *GNRHR* (Lin et al., 2006), and pedigrees of probands with HH can include individuals with delayed but otherwise normal puberty. However, more extensive analyses suggest that genetic variation in neither *GNRH* nor *GNRHR* is a common cause of late puberty in the general population (Sedlmeyer et al., 2005; Gajdos et al., 2008).

Research into the KISS-1/GPR54 system in both animal and human studies has identified it as a critical component of the HPG axis, necessary for pubertal onset. The first indications of the importance of the KISS-1/GPR54 signaling complex as a regulator of the HPG axis came in 2003 when two independent groups reported deletions and inactivating mutations of *GPR54* in patients with HH (de Roux et al., 2003; Seminara et al., 2003). Subsequently, activating mutations in this pathway were associated with precocious puberty in a report of central precocious puberty in the case of a female with an autosomal dominant mutation in *GPR54* (Teles et al., 2008). Thus, it is clear that activation of GPR54 by kisspeptins plays a pivotal role in the onset of puberty. It is not yet known, however, whether the KISS-1/GPR54 system is the initial trigger of puberty or whether it acts as a downstream effector of other yet to be identified regulatory factors (Seminara, 2007; Roth et al., 2007). Recently, mutations in *TAC3* and *TACR3* were identified in HH patients (Topaloglu et al., 2009). These genes encode neurokinin B and its receptor, which are highly expressed in the same neurons that express kisspeptin, further emphasizing the role of kisspeptin in the regulation of pubertal timing.

2.2. Kallmann syndrome

Several genes critical to HPG axis function and olfactory development have been identified through investigation of Kallmann syndrome (hypogonadotropic hypogonadism with anosmia/hyposmia). Mutations in Kallmann syndrome 1 (*KAL-1*) (Franco et al., 1991; Hardelin et al., 1993; Legouis et al., 1991) and fibroblast growth factor receptor 1 (*FGFR1*) (Dode et al., 2003) have been implicated in the X-linked and autosomal dominant forms of the disease, respectively, but appear to account for only approximately 20% of patients with KS (Dode et al., 2006). Recently, mutations in the prokineticin receptor-2 gene (*PROKR2*), a G-protein coupled receptor, and in its ligand prokinetcin-2 (*PROK2*) were identified in a cohort of KS patients (Dode et al., 2006), demonstrating that prokineticin signaling is important for olfactory and HPG axis development. One of the patients in this series was heterozygous for both a *PROKR2* mutation and a *KAL1* mutation, suggesting a possible digenic mode of inheritance (Dode et al., 2006). Finally, mutations in the nasal embryonic luteinizing hormone releasing hormone factor (*NELF*), which plays a role in migration of GnRH neurons and olfactory axon outgrowth (Kramer and Wray, 2000), have also been implicated in the pathogenesis of KS (Miura et al., 2004). A heterozygous deletion in *NELF* has been reported as a component, along with *FGFR1*, of digenic KS, but it is not clear whether mutations in *NELF* alone lead to KS (Pitteloud et al., 2007a).

The distinction among the different abnormalities of pubertal development may not be absolute. For example, mutations in *FGFR1* can cause both KS and HH (Pitteloud et al., 2006), and a homozygous mutation in *PROK2* has been reported to cause both KS and HH within a single kindred (Pitteloud et al., 2007b). A more comprehensive study of *PROK2* and *PROKR2* in HH and KS patients found mutations in both genes distributed in both groups of patients (Cole et al., 2008). Mutations in the *FGF8* gene, which encodes a ligand for *FGFR1*, have been observed in HH patients accompanied by variable olfactory phenotypes (Falardeau et al., 2008). Recently, mutations in *CHD7*, a gene responsible for CHARGE syndrome, which shares some developmental features with KS, were identified in patients with both normosmic HH and KS (Kim et al., 2008; Jongmans et al., 2009). Moreover, it has been reported that loss of function mutations in *FGFR1* can cause delayed puberty in members of HH pedigrees (Pitteloud et al., 2005, 2006), although variation in *FGFR1*