Patterns of Inheritance of Constitutional Delay of Growth and Puberty in Families of Adolescent Girls and Boys Referred to Specialist Pediatric Care

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Context and Objective: Constitutional delay of growth and puberty (CDGP), more commonly observed in boys than girls, often has a familial background. We characterized the occurrence of CDGP in relatives of CDGP patients to elucidate the mechanisms influencing timing of puberty.

Participants and Design: We identified 492 subjects with CDGP from hospital records of two pediatric clinics in Finland; 95 male and 29 female subjects and their first-degree relatives participated. In family members, CDGP was defined by use of growth charts (growth spurt taking place 2 SD beyond the mean). One third of the families was expanded to include also second-degree relatives with an interview-based assessment of pubertal timing.

Results: Of males, 80%, and of female probands, 75% had first-degree relatives with CDGP. Of all probands, 45% had one parent (unilineal families) and 32% had two parents affected. In 2% of the families, only siblings were affected. The prevalence of CDGP in male first-degree relatives was only slightly higher than in female relatives: 79 of 148 (53%) *vs.* 64 of 164 (39%), respectively ($P = 0.01$); male to female ratio was 1.2:1. In 74% of extended unilineal pedigrees (17 of 23), the inheritance pattern of CDGP was consistent with autosomal dominant inheritance.

Conclusions: CDGP clusters in families. Although its inheritance likely is complex, some predisposing genetic factors may have a dominant effect. CDGP was almost as common in male and female relatives of the CDGP subjects seen at specialist care, challenging the view of a marked overall male preponderance of CDGP. **(*J Clin Endocrinol Metab* 93: 723–728, 2008)**

Onset of puberty takes place across a wide range of ages in healthy adolescents (1–4). Precise mechanisms underlying regulation of onset of puberty are unknown, but based on the concordance of timing of its onset in monozygotic twins (5–10) and similarity in the timing of sexual maturation between family members (11), it appears that timing of puberty onset is genetically determined. Consequently, constitutional delay of growth and puberty (CDGP), which represents the extreme tail of the normal distribution, aggregates in families (12–15). Inheritance patterns of CDGP have, however, been addressed in only one study (16), in which the majority of the families displayed a pattern consistent with autosomal dominant inheritance. For first-degree relatives, the estimated relative risk for the onset of pubertal development 2 SD beyond the mean was 4.8 (95% confidence interval 2.2–19.8), compared with controls. Of note, pubertal timing was assessed through recall, a method that potentially produces imprecise data.

CDGP is defined as lack of any signs of puberty at an age 2.0 SD above the mean chronological age for puberty onset. CDGP should therefore be equally frequent in both genders. In clinical practice, CDGP is much more common in boys (16–19). Accordingly, at the other end of the normal variation in pubertal timing, idiopathic precocious puberty should also be equally frequent in both genders but is encountered more commonly in girls

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Abbreviations: CDGP, Constitutional delay of growth and puberty; phv, peak height velocity.

(20–22). In one study investigating familial patterns of precocious puberty, affected relatives of the probands were mostly female (22). The authors proposed that the segregation pattern of early puberty is consistent with autosomal dominant inheritance with gender-dependent penetrance. To our knowledge, no studies have compared the occurrence of CDGP in male and female family members of adolescents with CDGP.

In the present study, we assessed the timing of puberty in family members of probands with CDGP by retrospective analysis of the timing of pubertal components of linear growth using data collected from health records. This method provides an objective estimate of puberty timing in both genders. We explored the clustering of CDGP in both male and female relatives of a large number of probands with CDGP identified and referred to specialist pediatric care based on the recommendations of a nationwide screening program implemented in the Finnish school health care system. The Finnish well-baby clinics and school health care system were introduced already in the 1940s, and today the screening program has virtually 100% coverage of the population. We can therefore assume that the occurrence of CDGP in relatives of the probands identified with CDGP approximates the prevalence of CDGP in both genders in the general population. We also investigated whether degree of pubertal delay or other physical characteristics differed between probands with familial background of CDGP and sporadic subjects.

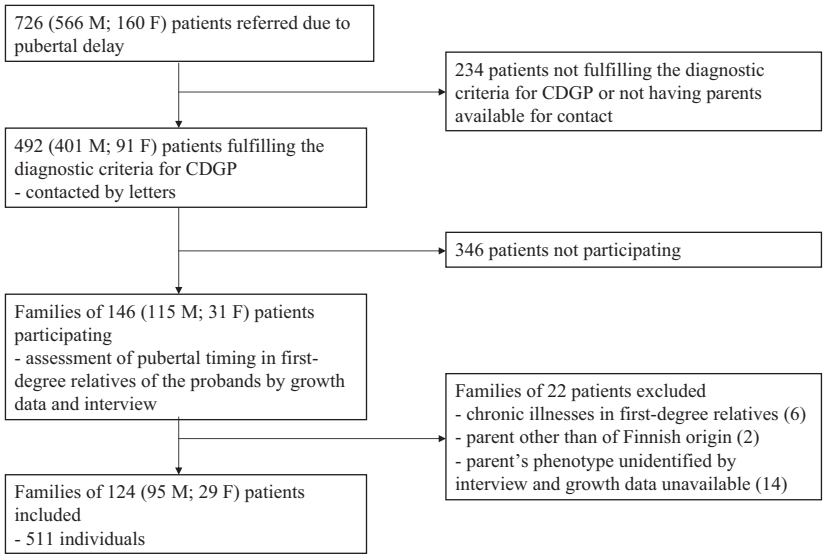

FIG. 1. Enrollment of study subjects (M, male; F, female) with CDGP and their family members from all patients referred to specialist pediatric clinics due to pubertal delay during 1982–2004.

Subjects and Methods

Subject population

Boys and girls diagnosed with CDGP were gathered through the medical records of adolescents referred to specialist pediatric care at the Hospital for Children and Adolescents, Helsinki University Hospital, and at Jorvi Municipal Hospital, Espoo, Finland, between the years 1982 and 2004. Most of the adolescents with late puberty had been referred because of delay in pubertal development detected by the nationwide screening program implemented in the Finnish school health care system since the 1960s. This screening program includes regular height and weight measurements and staging of pubertal development at critical ages with recommendations to refer boys failing to achieve Tanner genital stage II by age 13.5 yr and girls not achieving Tanner breast stage II by age 13.0 (23). When records of 726 patients with the diagnosis coding of delayed puberty were investigated, 68% (492 subjects) fulfilled the true diagnostic criteria for CDGP (given below) and had both parents available for contact (Fig. 1). Medical history, clinical examination, or routine laboratory tests (blood cell count, thyroid, kidney and liver function tests, gonadotropins and sex steroids, and laboratory tests excluding chronic infections and celiac disease) failed to reveal any signs of chronic illnesses accounting for their delayed puberty. IGF-I levels were measured and GH stimulation tests performed if the IGF-1 level or growth pattern suggested for GH deficiency. Hypogonadotropic hypogonadism, if suspected, was excluded by GnRH testing and clinical follow-up, ensuring spontaneous pubertal development. Patients were contacted by a letter asking primarily their parents and siblings to participate. These first-degree relatives received questionnaires about their pubertal development. Their archived growth records were retrieved and all individuals in participating families were interviewed by phone. Families were excluded if first-degree relatives had any chronic illnesses that could have affected growth or development or if pubertal timing could not be assessed in one of the parents. Only families with Finnish origin were included because growth records were usually not available for individuals originating outside Finland. In addition, because the inheritance pattern of CDGP is likely to be complex, we also aimed at keeping the study population as homogenous as possible by including families of Finnish origin only.

Eventually, the analysis included 124 families (of 95 male and 29 female probands), which represented 25% of the families of all eligible subjects. The number of probands' first-degree relatives was 387, including 248 parents and 139 postpubertal siblings (58 brothers, 81 sisters). Second-degree relatives, such as aunts, uncles, and grandparents, and third-degree relatives, such as cousins, great-grandparents, and even fourth-degree relatives of the probands were successfully recruited in 30% of the families (37 of 124), first by phone based on permission obtained from parents of the proband and then by letters including similar questionnaires that were mailed to first-degree relatives. We did not suspect or verify consanguinity in any of the families. The total numbers of investigated male and female family members of the probands were 290 and 304. Altogether, 718 individuals participated, including the probands.

In the 95 male probands, the mean (± SD) age for acceleration of pubertal height growth (take-off, see below) was 14.97 (± 0.65) yr, and in 29 female probands 12.96 (± 0.84) yr, more than 3.4 and 2.8 SD later than the average in boys and girls (3). Tanner genital stage II (testicular volume of more than 3 ml) was first observed at the mean age of 15.10 (± 0.83) yr, more than 3.4 SD later than the average for Finnish boys (24). Tanner breast stage II was observed at the mean age of 13.75 (± 0.71) yr, more than 2.3 SD later than the average for Finnish girls (24). Delay in bone maturation at the initial evaluation in 89 boys was 2.6 (± 0.7) yr and in 27 girls, 2.7 (±1.0) yr.

Protocol

The study protocol was approved by the Ethics Committee for Pediatrics, Adolescent Medicine, and Psychiatry, Hospital District of Helsinki and Uusimaa. All participants or their parents/guardians or both provided written informed consent. The timing of puberty in first-degree relatives was estimated from growth data by analysis of the timing of pubertal components of linear growth such as age at pubertal acceleration of growth (take-off) and age at peak height velocity (phv). Age at

take-off was estimated from the point at which growth velocity increased after the slowest growth velocity at the beginning of the pubertal growth spurt, resulting in more than 0.3 SD increase in height SD score. Age at phv was estimated from the point at which growth velocity was fastest during puberty by inspecting the point of steepest slope in linear growth (25). Criteria for CDGP were set by use of one or both of the following: age at take-off or phv occurring 2 SD beyond the mean, specifically age at take-off later than 13.8 and 12.2 yr, or age at phv later than 15.6 and 13.7 yr in males and females (3).

Timing of puberty for all study participants was also evaluated by structured interview (26) including questions about possible pubertal delay in second- or third-degree relatives of the proband. If the interview suggested CDGP also being present in second- or third-degree relatives, these relatives were recruited for the study, with the permission of the parents of the probands. Objective assessment of the timing of puberty, based on growth data, was possible in 83% of the nuclear family members and 40% of relatives of the second degree or more. If growth charts were unavailable, timing of puberty was based on interviews. In that case, criteria for CDGP were recalling having undergone pubertal development more than 2 yr later than their peers (both sexes) or menarche after 15 yr. Possible chronic illnesses and other factors in childhood possibly affecting growth and development underwent careful discussion.

Based on pubertal timing in first-degree relatives, the probands were grouped as familial (at least one affected first-degree relative) or sporadic (no affected first-degree relatives). According to the number of affected parents and available data on second- or third-degree relatives, the familial probands were further subdivided into three groups: 1) unilineal families (only one affected parent and no evidence for CDGP in the other parent or his/her first-degree relatives); 2) bilineal families (either both parents themselves affected or an unaffected parent having an affected sibling or parent); and 3) families with unaffected parents (one or more siblings affected). To evaluate further the inheritance pattern of CDGP, among 37 extended pedigrees, 23 with unilineal background were explored. The other 14 extended pedigrees were bilineal and were not included in the inheritance pattern analysis because the presence of two affected parents makes the determination of the mode of inheritance difficult. In relatives of all probands with a positive family history of CDGP, we calculated the occurrence of CDGP in males and females, first in first-degree relatives with puberty-timing assessment mostly by growth data and then also including second-, third-, or fourth-degree relatives whose pubertal timing assessment was mostly recall based. We also calculated the occurrence of CDGP separately in parents and siblings of the male and female probands with unilineal backgrounds. In these families, the proportions of paternal and maternal inheritance of CDGP can be compared and also the occurrence of CDGP in male *vs.* female siblings evaluated.

Physical characteristics, such as birth length, height before puberty (at the age 7 yr), minimum relative height at puberty (the lowest observed height SD at the beginning of pubertal growth spurt), age at minimum relative height, body mass index at age 7 yr and at minimum relative height, maximum delay of bone maturation (the greatest observed difference between bone age and calendar age during follow-up), age at take-off, and age at attaining Tanner stage 2 were all compared between probands with a familial background of CDGP and sporadic CDGP subjects.

Statistical analysis

The statistical package for social sciences (release number 11.0.1; SPSS, Chicago, IL) served for statistical analysis. The Pearson χ^2 test served to compare the proportions of individuals meeting the criteria for CDGP. Comparison of the parameters between sporadic CDGP subjects and probands with a familial background of CDGP was performed by the independent sample *t* test. $P < 0.05$ was considered significant.

Results

Familial clustering of CDGP

A positive family history of CDGP was evident in 79% of the probands (98 of 124) (Fig. 2). Male and female probands had affected first-degree relatives equally often: 76 of 95 for males (80%) and 22 of 29 for females (76%). Most commonly the families with multiple CDGP had one affected parent (unilineal families) (Fig. 3A). This was found in 46% of the families of male probands and 41% of the families of female probands. In 33 and 31% of the families of male and female probands, respectively, both parents were affected (bilineal families) (Fig. 3B). Of these 40 families classified as bilineal, nine (23%) were so by extension, *i.e.* the unaffected parent had a first-degree relative with CDGP (Fig. 3C). Families with only siblings affected were rare, representing only 2% of all families (Fig. 3D). Sporadic CDGP was found in 26 families of 19 male and seven female probands. In these sporadic families, none of the 75 first-degree relatives had CDGP, and parental interviews revealed only one first cousin with CDGP in one pedigree but no other affected second- or third-degree relatives. Probands with sporadic and familial CDGP had similar physical characteristics (Table 1).

Of 23 extended unilineal families (Fig. 2), CDGP was verified in three generations in 16 (70%), and 17 (74%) displayed an inheritance pattern of CDGP consistent with autosomal domi-

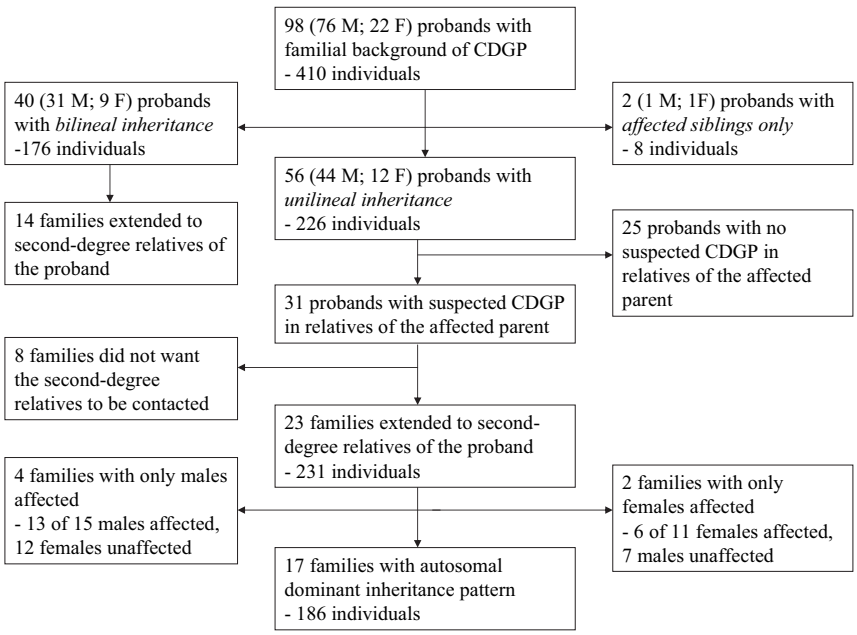

FIG. 2. Familial clustering patterns of CDGP in 98 of 124 families of probands (79%) (M, male; F, female) with at least one first-degree relative with CDGP. Proportions of probands and total number of investigated individuals in unilineal families (only one affected parent and no evidence for CDGP in the other parent or his/her first-degree relatives), bilineal families (either both parents themselves affected or an unaffected parent having an affected sibling or parent), and families with no affected parents (one or more siblings affected) are shown. The enrollment of second-, third-, and fourth-degree relatives and the proportions of families with autosomal dominant inheritance pattern, as evidenced by affected pedigree members of both sexes transmitting CDGP to roughly 50% of their offspring, are also presented.

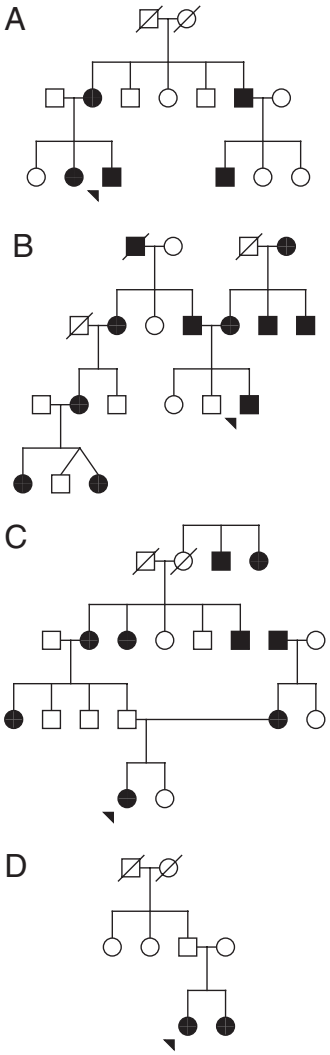

FIG. 3. Examples of pedigrees of adolescents (proband, *arrowhead*) with CDGP referred to specialist pediatric care. Affected individuals with more than 2 SD later than average pubertal growth spurt, or recalled 2 yr later than average puberty (●/■), unaffected individuals (○/□). A, Male proband with only one affected parent and affected relatives of both sexes transmitting CDGP to roughly half of their offspring (unilineal autosomal dominant inheritance). B, Male proband with two affected parents (bilineal inheritance). C, Female proband with one parent affected and the other parent unaffected but having relatives with CDGP (bilineal inheritance by extension). D, Female proband with an affected sibling only.

nant inheritance, as evidenced by affected pedigree members of both sexes transmitting CDGP to roughly 50% of their offspring (Fig. 3A). In all 23 extended unilineal pedigrees, 49% of the family members (91 of 186), including the probands, were affected.

Proportions of affected male and female relatives

Male first-degree relatives of all probands with a familial background of CDGP were only slightly more often affected than were female relatives (Table 2). The male to female ratio for first-degree relatives was 1.2:1. When the second-, third-, and fourth-degree relatives were included in the analysis, an equal proportion of affected male and female relatives was found.

The gender-specific occurrence of CDGP was investigated separately in parents and siblings of all probands with an unilineal background. CDGP tended to be more common in brothers than sisters of the probands, but this difference was not quite significant: nine of 27 (33%) *vs.* five of 37 (14%) ($\chi^2 = 3.59$, $P = 0.06$) (Table 3). Mothers of all probands were equally often affected with CDGP as were these families' fathers: 32 of 56 (57%) *vs.* 24 of 56 (43%) ($\chi^2 = 2.29$, $P = 0.13$). Mothers were more often affected than the sisters of the probands: 32 of 56 (57%) *vs.* five of 37 (14%) ($\chi^2 = 17.7$, $P < 0.01$). CDGP criteria were met equally often in fathers and brothers of the probands: 24 of 56 (43%) *vs.* nine of 27 (33%) ($\chi^2 = 0.69$, $P = 0.41$). Male and female probands equally often had an affected father or mother, and no significant difference appeared between male and female probands in their numbers of affected brothers or sisters.

Discussion

Based on studies in twins, genetic factors account for 50–80% of all variation in pubertal timing (5–10). Genetic factors are thus likely to contribute to the propensity for CDGP, an extreme variant of normal pubertal timing. It has long been known that CDGP runs in families (12–15), although until now only one extended study has addressed the segregation of CDGP in families (16). That study, however, assessed pubertal development based on recall, a method that may introduce inaccuracy. Our study offers an objectively assessed evaluation of CDGP in families of probands because diagnoses in the nuclear families relied on information on growth data from health records. Because acceleration of pubertal growth is a consequence of the onset of central puberty (1–4), it can therefore serve in estimating puberty timing. One third of the families participating in our study was extended to include second-, third-, or fourth-degree relatives, and only in the majority of these subjects, the assessment of pubertal timing was based on interviews. In total, compared with 53 families and more than 400 individuals explored by Sedlmeyer *et al.* (16), we assessed the timing of puberty onset in 124 families of CDGP patients including more than 700 individuals.

Here we found that CDGP has a strong familial component with a familial occurrence of roughly 80%. Based on the used definition of CDGP, *i.e.* 2 SD delay of pubertal growth spurt, 2.5% of the relatives of the probands can be expected to be affected by chance. Therefore, in the present study, we would anticipate identifying 10 CDGP patients of the 387 first-degree relatives participating. The observed number of 143 affected first-degree relatives with a 2 SD delay of growth spurt clearly exceeds the expectation, being 15 times higher than expected by chance. Equal proportions of both genders showed a positive CDGP family history. The majority of the Sedlmeyer group's pedigrees showed an inheritance pattern compatible with autosomal dominant inheritance (16). Our data also suggest that a dominant mode of inheritance is common among the pedigrees segregating CDGP. The large proportion of families appearing dominant may include some selection bias. Parents with delayed puberty may have been more willing to participate than parents with normal puberty timing. On the other hand, because more remote relatives in the families with sporadic CDGP were not explored, the prevalence of sporadic CDGP may have been over-

TABLE 1. Physical characteristics (± SD) of probands with (familial) and without (sporadic) CDGP in first-degree relatives

	Sporadic male probands (n = 19)	Familial male probands (n = 76)	Sporadic female probands (n = 7)	Familial female probands (n = 22)
Length at birth (cm)	50.7 ± 1.5 (n = 14)	50.3 ± 2.6 (n = 60)	50.7 ± 2.7 (n = 7)	50.1 ± 2.2 (n = 20)
Height at age 7 yr (SD)	−0.59 ± 0.80 (n = 17)	−0.62 ± 0.96 (n = 75)	−0.65 ± 1.23 (n = 6)	−0.61 ± 1.32 (n = 22)
Body mass index at age 7 yr (kg/m^2)	16.18 ± 1.72 (n = 18)	15.62 ± 1.62 (n = 74)	15.19 ± 0.85 (n = 7)	15.43 ± 1.94 (n = 22)
Minimum relative height at puberty (SD)[a]	−1.81 ± 0.67 (n = 17)	−1.65 ± 0.95 (n = 72)	−1.80 ± 1.12 (n = 7)	−1.96 ± 1.30 (n = 21)
Age at minimum relative height (yr)	15.10 ± 0.69 (n = 17)	15.23 ± 0.66 (n = 73)	13.29 ± 0.73 (n = 7)	13.36 ± 0.61 (n = 20)
Body mass index at minimum relative height (kg/m^2)	20.56 ± 3.03 (n = 19)	19.48 ± 3.77 (n = 75)	17.29 ± 1.25 (n = 7)	17.20 ± 2.72 (n = 22)
Age at acceleration of pubertal height growth (yr)	14.69 ± 0.42 (n = 15)	14.97 ± 0.66 (n = 75)	12.70 ± 0.61 (n = 7)	12.94 ± 0.87 (n = 22)
Maximum delay in bone maturation (yr)[b]	2.4 ± 0.8 (n = 18)	2.6 ± 0.7 (n = 71)	3.2 ± 0.9 (n = 6)	2.5 ± 1.0 (n = 21)
Age at attaining Tanner stage 2 (yr)	15.24 ± 0.57 (n = 10)	15.13 ± 0.83 (n = 52)	13.79 ± 0.70 (n = 4)	13.84 ± 0.70 (n = 15)

No significant differences between familial and sporadic probands appeared in any parameters.

[a] The lowest observed height SD in the beginning of pubertal growth spurt.

[b] The greatest observed difference between bone age and calendar age during follow-up.

estimated as well. By physical characteristics, our sporadic CDGP subjects could not be distinguished from other probands; degree of pubertal delay and patterns of growth, as well as body mass index reflecting obesity, were similar. We expected to observe more overweight subjects among sporadic than familial male probands because obesity may delay onset of puberty in boys (27). However, the prevalence of obesity between familial and sporadic subjects did not differ.

An issue that has been addressed only occasionally (28) is the apparent contradiction between the statistical definition of CDGP (onset of puberty 2 SD beyond the mean), and the frequent report that CDGP is more common among boys (16–19). We aimed at addressing this discrepancy by studying the clustering of CDGP, using growth chart-based assessments, in both genders of family members of pedigrees segregating CDGP. In previous reports, the male to female ratio among CDGP patients has ranged from 2:1 to 5:1 (16–19). In our study, three quarters of the identified probands were male. A comparable male preponderance of CDGP was, however, undetectable among affected first-degree relatives. Although the proportion of affected males was somewhat larger than that of females, the male to female ratio was only 1.2:1, strikingly different from the probands' 3:1.

Finding almost equal proportions of affected male and female relatives points to the possibility that the marked overrepresentation of boys with CDGP at pediatric clinics may be biased. The fact that the first signs of puberty are more easily detected in girls (breast budding *vs.* testicular enlargement), in addition to the later pubertal growth spurt in boys (3), may skew the practice toward more frequent referral of boys, although the recommendation is to refer both genders with first signs appearing more than 2 SD beyond the mean, *i.e.* after age 13.5 in boys and 13.0 in girls. As a consequence of skewed referral practice generating male predominance of CDGP, one would expect referred girls to show more severe delay of puberty. In one study based on retrospective evaluation of hospital charts of adolescents referred to an endocrinology clinic for pubertal delay, the girls were more severely affected, as evidenced by their greater bone age delay (18). We saw no difference in delay of bone maturation between male and female probands (mean delay of 2.6 yr in boys and 2.7 yr in girls). The explanation for the higher ratio of boys to girls seen in pediatric clinics may therefore also relate to boys' keener interest in athletic performance and physical characteristics around puberty (29), for which reason they may request further investigations themselves irrespective of referral practices.

Based on age at menarche (11, 30) and age at onset of breast development (31), girls of some ethnic/racial groups may mature earlier than previously. Earlier pubertal development has not, however, been suggested in boys (32–34). Such sexual dimorphism in a secular trend toward earlier puberty could also influence the sex distribution of CDGP patients. Normative data currently used for the cutoff age limits of normal pubertal maturation are based on a study by Marshall and Tanner (1, 2) of British children in the 1960s. A decrease in the ages that correspond to the 2 SD later-than-average onset of puberty in the female population exclusively would mean identification of fewer girls than boys with CDGP. As a consequence, this could explain the male preponderance of CDGP seen in pediatric clinics. Our study, using the same criteria for CDGP in all females and all males, irrespective of year of birth, showed that mothers of the probands had CDGP far more often than did the sisters, whereas the proportions of affected fathers and brothers were similar. Whether a sexual dimorphism in a trend toward earlier puberty is an explanation for our finding remains unsolved.

TABLE 2. Prevalence of CDGP in male and female relatives of all probands with a familial background of CDGP (at least one affected first-degree relative)

	Males	Females
First-degree relatives	79 of 148 (53%)[a]	64 of 164 (39%)[a]
All relatives	133 of 265 (50%)	128 of 290 (44%)

[a] $\chi^2 = 6.46$, $P = 0.01$ between genders.

TABLE 3. Prevalence of CDGP in first-degree relatives of probands with a unilineal background of CDGP (only one affected parent and no evidence for CDGP in the other parent or his/her first-degree relatives)

	Female probands	Male probands	All probands
Fathers	7 of 12 (58%)	18 of 44 (41%)	24 of 56 (43%)
Mothers	5 of 12 (42%)	26 of 44 (59%)	32 of 56 (57%)[a]
Male siblings	0 of 5 (0%)	6 of 19 (32%)	9 of 27 (33%)
Female siblings	2 of 10 (20%)	3 of 24 (13%)	5 of 37 (14%)[a]

[a] $\chi^2 = 17.7$, $P < 0.01$ between mothers and female siblings.

In conclusion, our data, based on analysis of growth charts of most first-degree relatives of CDGP patients, suggest that CDGP in both genders is almost equally common. The marked male predominance of CDGP in clinical practice may therefore, at least in part, be a consequence of referral bias. A female-specific secular trend toward earlier puberty may also contribute to the overrepresentation of CDGP in boys. Longitudinal population-based studies must, however, determine whether the puberty onset in girls truly has shifted. The strong familial background of CDGP in both sexes indicates that this trait is influenced by genetic factors, some of which may have dominant modes of action. Future investigations of the molecular mechanisms, and identification of those genes that underlie CDGP would improve our understanding of factors regulating onset of normal puberty.

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