Annals of human genetics

doi: 10.1111/j.1469-1809.2010.00606.x

Association of Linear Growth Impairment in Pediatric Crohn's Disease and a Known Height Locus: A Pilot Study

Jessica J. Lee[1]*, Jonah B. Essers[1,2], Subra Kugathasan[3], Johanna C. Escher[4], Guillaume Lettre[5], Johannah L. Butler[6], Michael C. Stephens[7], Marco F. Ramoni[8,9], Richard J. Grand[1,10] and Joel Hirschhorn[2,6]

[1] *Division of Gastroenterology and Nutrition, Children's Hospital Boston, Boston, MA 02115, USA*
[2] *Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA*
[3] *Division of Pediatric Gastroenterology, Emory University School of Medicine, Atlanta, GA 03022, USA*
[4] *Department of Pediatric Gastroenterology, Erasmus MC- Sophia Children's Hospital, Rotterdam, the Netherlands*
[5] *Montreal Heart Institute, Quebec, Canada*
[6] *Divisions of Genetics and Endocrinology and Program in Genomics, Children's Hospital Boston, Boston, MA 02115, USA*
[7] *Division of Gastroenterology and Nutrition, Children's Hospital of Wisconsin, Milwaukee, WI 53226, USA*
[8] *Children's Hospital Informatics Program, Children's Hospital Boston, Boston, MA 02115, USA*
[9] *Harvard-MIT Division of Health Sciences and Technology, Harvard Medical School, Boston, MA 02115, USA*
[10] *Clinical and Translational Study Unit, Children's Hospital Boston, Harvard Medical School, Boston, MA 02115, USA*

Summary

The etiology of growth impairment in Crohn's disease (CD) has been inadequately explained by nutritional, hormonal, and/or disease-related factors, suggesting that genetics may be an additional contributor. The aim of this cross-sectional study was to investigate genetic variants associated with linear growth in pediatric-onset CD. We genotyped 951 subjects (317 CD patient–parent trios) for 64 polymorphisms within 14 CD-susceptibility and 23 stature-associated loci. Patient height-for-age Z-score < -1.64 was used to dichotomize probands into growth-impaired and nongrowth-impaired groups. The transmission disequilibrium test (TDT) was used to study association to growth impairment. There was a significant association between growth impairment in CD (height-for-age Z-score < -1.64) and a stature-related polymorphism in the dymeclin gene *DYM* (rs8099594) (OR = 3.2, CI [1.57–6.51], $p = 0.0007$). In addition, there was nominal over-transmission of two CD-susceptibility alleles, 10q21.1 intergenic region (rs10761659) and *ATG16L1* (rs10210302), in growth-impaired CD children (OR = 2.36, CI [1.26–4.41] $p = 0.0056$ and OR = 2.45, CI [1.22–4.95] $p = 0.0094$, respectively). Our data indicate that genetic influences due to stature-associated and possibly CD risk alleles may predispose CD patients to alterations in linear growth. This is the first report of a link between a stature-associated locus and growth impairment in CD.

Keywords: Height, growth retardation, inflammatory bowel disease, *DYM*, dymeclin

Introduction

Growth impairment is a major complication of pediatric-onset Crohn's disease (CD) and occurs in 19–35% of affected children (Puntis et al., 1984; Griffiths et al., 1993; Kirschner, 1993; Motil et al., 1993; Hildebrand et al., 1994; Markowitz & Daum, 1994). Growth impairment in CD has traditionally been attributed to nutritional, hormonal, and disease-related factors, such as inflammation, disease severity, and the use of corticosteroids. However, a recent study suggests that growth delay persists for at least 2 years after the diagnosis in many prepubertal children with CD despite improved disease activity and the frequent use of immunomodulators and biologics (Pfefferkorn et al., 2009). A previous study of growth in CD patients revealed that those who were not growth impaired at diagnosis did not subsequently develop growth impairment during a 3-year follow up (Motil et al., 1993).

*Corresponding author: Jessica J. Lee, MD, MMSc, Division of Gastroenterology, Children's Hospital Boston, 300 Longwood Avenue, Boston, Massachusetts 02115. Tel: (617) 355–2962; Fax: (617) 730–0494; E-mail: Jessica.lee@childrens.harvard.edu

© 2010 The Authors
Annals of Human Genetics © 2010 Blackwell Publishing Ltd/University College London

Identifying early those individuals who will suffer from permanent growth impairment would allow physicians to formulate an individualized therapy to preserve the patient's linear growth. Accordingly, such children might benefit from nontraditional therapy, such as first-line anti-TNF-α antibody, aggressive nutritional therapy, and/or growth hormone supplementation (Borrelli et al., 2004; Knight et al., 2005; Walters et al., 2007; Heyman et al., 2008).

There exists a clear role for genetic predisposition in CD, which exhibits familial clustering and a significantly higher concordance rate in monozygotic compared to dizygotic twins (Tysk et al., 1988). Early age at diagnosis is associated with more complicated disease (Van Limbergen et al., 2008) and a greater likelihood of having affected family members (Polito et al., 1996). Moreover, offspring of affected CD parents develop CD at an earlier age (Polito et al., 1996; Grandbastien et al., 1998; Lee et al., 1999). These findings suggest that pediatric-onset CD represents a subphenotype of the disease, which may result from susceptibility variants that have a larger effect size. Over the past decade, more than 40 CD-susceptibility genetic loci have been identified and replicated through linkage and genome-wide studies in adult and pediatric patients (Barrett et al., 2008; Kugathasan et al., 2008; Essers et al., 2009; Imielinski et al., 2009). Except for *NOD2* and *ATG16L1* mutations (Russell et al., 2005; Prescott et al., 2007), the impact of these susceptibility loci have not yet been directly associated with specific phenotypes.

Height is a highly heritable trait (Preece, 1996), and multiple genetic variants associated with stature have already been reported in the general population (Weedon et al., 2007; Lettre et al., 2008; Sanna et al., 2008; Weedon et al., 2008; Weedon & Frayling, 2008; Lettre, 2009). In CD, published studies have investigated genetic variants associated with growth impairment: patients with an *OCTN1/2* (now known as SLC22A4/A5) haplotype had lower height at diagnosis (Russell et al., 2006); patients with *IL6* -174 GG genotype had lower height Z-scores compared to those with GC or CC genotypes (Sawczenko et al., 2005); and patients carrying *TNF-α* promoter polymorphisms with loss of function had higher mean height z-scores (Levine et al., 2005). However, the association of these genetic variants with growth impairment has not yet been confirmed. We hypothesized that, in addition to inflammation and nutrition, growth impairment often seen in CD children is modulated by CD-susceptibility and/or stature-associated alleles that affect the general population. Accordingly, our aims of the present pilot study were to (1) compare the difference in transmission of known CD-susceptibility and stature-associated alleles in growth-impaired and nongrowth-impaired children with CD; and (2) determine if genetic variants previously reported to affect linear growth in European CD populations also affect the US children with CD.

Materials and Methods

Subjects

This was a cross-sectional pilot study investigating genetic variants related to linear growth impairment in pediatric-onset CD. We recruited 317 Caucasian patients (60.8% males) diagnosed with CD between the ages 1–18 and their biological parents from two tertiary care pediatric centers, Children's Hospital Boston and Children's Hospital of Wisconsin. Of the recruited trios, 166 were from Boston and 151 from Wisconsin. Inclusion criteria included verification of CD diagnosis using clinical, endoscopic, histopathologic, and radiographic studies prior to enrollment (Silverberg et al., 2005).

Description of the Study Visit

On the day of the study visit, we measured heights of all subjects using a wall-mounted Holtain stadiometer either at Children's Hospital Boston or Children's Hospital of Wisconsin. We also obtained clinical information pertaining to CD from patients and families, which we verified using the medical record. Height at diagnosis was not available for all patients since some were diagnosed elsewhere prior to being referred to our tertiary care centers. As a result, we also recorded all available retrospective heights measured in the same fashion during clinic visits at these two institutions, and calculated mean height for each patient. Tanner stage was not available for most patients, and therefore, was not included. The mean heights were converted into standard deviation scores (Z-scores) for all patients using the National Center for Health Statistics reference values. For those subjects whose heights were measured after 18 years of age, their heights were converted to the same Z-scores calculated for gender-matched persons who are 17.9 years of age. Presence of growth impairment was defined as a mean height-for-age Z-score < -1.64 (equivalent to <5th percentile on the growth curve). We also collected peripheral venous blood, from which lymphocytic DNA was extracted according to the manufacturer's instructions using the Gentra Puregene Blood Kit (Qiagen, Inc., Valencia, CA).

Genotyping

We selected for genotyping loci associated with CD risk and adult height variation at the time we designed this experiment in 2007. This list includes 14 confirmed CD and 23 known stature-associated loci selected from prior publications by others (Hugot et al., 1996; Rioux et al., 2001, 2007; Peltekova et al., 2004; Potocnik et al., 2004; Stoll et al., 2004; Duerr et al., 2006; Browning et al., 2007; Hampe et al., 2007; Libioulle et al., 2007; Parkes et al., 2007; Weedon et al., 2007; Wellcome Trust Case Control Consortium, 2007; Lettre et al., 2008). Thirty-three SNPs from 14 CD-susceptibility genes or nearby genes of interest, and one SNP from each stature-associated locus were included. For some of the CD-susceptibility loci, we included

© 2010 The Authors
Annals of Human Genetics © 2010 Blackwell Publishing Ltd/University College London

more than one SNP if prior genome-wide association studies reported multiple SNPs within or near the variant. However, we chose only one SNP per stature-associated locus as previously published (Lettre et al., 2008). In addition, we included eight SNPs within the *OCTN 1/2*, *IL6*, and *TNF-α* promoter regions that have been reported to be associated with growth retardation in CD patients in prior studies (Levine et al., 2005; Sawczenko et al., 2005; Russell et al., 2006). The complete list of 64 SNPs genotyped in this study is listed in Table S1. Genotyping was performed using the platform iPLEX Sequenom MassARRAY system (Sequenom, Inc., San Diego, CA).

Statistical Methods

We dichotomized patients into one of two groups: growth-impaired and nongrowth-impaired, based on their mean height-for-age Z-scores. We used two-sample *t*-tests and Wilcoxon rank sum tests to assess differences in demographic and clinical characteristics of the two groups. The SPSS statistics package version 17.0 (SPSS Inc, Chicago, IL) was used for phenotypic analysis. In order to assess generalizability, we analyzed our cohort for association with known CD-susceptibility loci by transmission disequilibrium testing (TDT) using the PLINK statistical package, http://pngu.mgh.harvard.edu/purcell/plink/ (Purcell et al., 2007). The TDT avoids the possibility of spurious associations due to population stratification. Differences in genotype frequency were analyzed using the χ^2 test. Subsequently, each CD-susceptibility and stature-related SNP was analyzed for association with the presence or absence of growth impairment, also using the TDT. We performed Benjamini–Hochberg false discovery rate analysis to account for multiple hypothesis testing (Benjamini & Hochberg, 1995). Then, we calculated heterogeneity p-values to assess whether transmission of the risk alleles is significantly different between growth-impaired and nongrowth-impaired CD patients.

Ethical Considerations

The institutional review boards (IRB) at Children's Hospital Boston and Children's Hospital of Wisconsin approved the study protocol. Prior to enrollment into the study, informed consent was obtained from subjects who were at least 18 years of age, and parental consent was obtained from subjects who were 17 years or younger.

Results

Patient Characteristics

A total of 951 subjects, or 317 CD affected child–parent–parent trios, were enrolled into our study. All patients in this cohort identified themselves as descendents of European ancestry. The median age at diagnosis of inflammatory bowel disease (IBD) was 12.0 years (interquartile range (IQR) 10–14). Sixty-five patients (20.5%) met the criteria for growth impairment based on mean height-for-age Z-score < -1.64. These data are similar to ours and other studies (Griffiths et al., 1993; Motil et al., 1993; Lee et al., 2010). Except for the difference in mean height Z-scores, the remaining demographic data are similar between the two growth groups (Table 1).

As shown in Table S2, the majority of patients in both growth groups had ileocolonic disease with or without upper gastrointestinal involvement (Montreal Classification disease location L3 or L3+L4) and nonstricturing and nonpenetrating disease behavior (Montreal Classification disease behavior B1 or B1p) as previously reported (Van Limbergen et al., 2008). Due to the pilot nature of this study, attempts to calculate prevalence or absence of growth impairment for specific disease-related phenotype were not possible. However, our previously reported cohort representing a similar patient population demonstrated no significant relationship between persistent growth impairment and disease-associated factors (Lee et al., 2010).

Genetic Analyses

Our data met the quality control measures, including genotyping rate ≥98% and Mendelian inheritance error of 0.1%. Deviation from Hardy–Weinberg equilibrium was not observed for any of the 64 SNPs. Our primary aim focused exclusively on association between the growth impairment phenotype and presence or absence of CD-susceptibility and/or stature-related SNPs. We did not intend to correlate phenotypes relating to disease location and behavior with genotypes due to the small sample size.

As shown in Table 2, the TDT confirmed an association between CD phenotype and many of the already-validated CD SNPs previously described by others, including

Table 1 Demographic and clinical characteristics of patients based on growth status

	Growth-impaired ($N = 65$)	Nongrowth-impaired ($N = 252$)
Males (%)	41 (63.1)	155 (61.5)
Median age of diagnosis [IQR]	11.0 [9.0, 13.0]	12.0 [9.5, 14.5]
Mean height Z-score (SD)	−2.36 (0.62)	−0.19 (0.96)

IQR = interquartile range, SD = standard deviation.

© 2010 The Authors
Annals of Human Genetics © 2010 Blackwell Publishing Ltd/University College London

Table 2 TDT of Crohn's disease-susceptibility loci in the study cohort

Chr	Gene	SNP	Risk Allele	T	U	OR [CI]	P-value
16q12	*NOD2*	rs2066845	C	35	12	2.92 [1.51–5.62]	0.0008
10q21.1	intergenic	rs10761659	G	174	117	1.49 [1.18–1.88]	0.0008
1p31	*IL23R*	rs11209026	A	16	37	0.43 [0.24–0.78]	0.0039
1p31	*IL23R*	rs7517847	T	166	119	1.39 [1.10–1.77]	0.0054
5q31	*OCTN1/2*	rs17622208	A	173	129	1.34 [1.07–1.69]	0.0113
16q12	*NOD2*	rs2066844	T	38	19	2.00 [1.15–3.47]	0.0119
3p21	*BSN*	rs9858542	A	164	122	1.34 [1.06–1.70]	0.0130
5p13	*PTGER4*	rs4495224	A	157	116	1.35 [1.06–1.72]	0.0131
2q37	*ATG16L1*	rs2241880	G	168	126	1.33 [1.06–1.68]	0.0143
6p	*TNF-α*	rs1799724	T	44	70	0.63 [0.43–0.92]	0.0149
1p31	*IL23R*	rs11805303	T	142	104	1.37 [1.06–1.76]	0.0154
2q37	*ATG16L1*	rs10210302	T	159	121	1.31 [1.04–1.66]	0.0232
5q31	*OCTN1/2*	rs1050152	T	176	136	1.29 [1.04–1.62]	0.0235
5q31	*OCTN1/2*	rs11739135	C	163	127	1.28 [1.02–1.62]	0.0345
16q12	*NOD2*	rs17221417	G	146	113	1.29 [1.01–1.65]	0.0403
5q33	*IRGM*	rs1000113	T	70	48	1.46 [1.01–2.11]	0.0428

Chr = chromosome, SNP = single nucleotide polymorphism, T = transmitted, U = untransmitted, OR = odds ratio, CI = confidence interval.

NOD2, 10q21.1 intergenic region, *IL23R*, *OCTN1/2*, and *ATG16L1* (Hugot et al., 1996; Rioux et al., 2000, 2001, 2007; Peltekova et al., 2004; Duerr et al., 2006; Hampe et al., 2007; Wellcome Trust Case Control Consortium, 2007). The *IL23R* SNP, rs11209026, was also found to be protective in our cohort as previously reported (OR = 0.43, CI [0.24–0.78], p = 0.0039) (Duerr et al., 2006). None of the height-related SNPs were associated with the diagnosis of CD in the absence of stratification according to height.

We then looked at the association between growth impairment in CD and transmission of CD-risk and stature-related loci. As shown in Table 3, we observed over-transmission of the stature-related SNP in the dymeclin gene *DYM* (rs8099594) from the heterozygous parents to growth-impaired children with CD (height-for-age Z-score < -1.64) compared to those who were not growth impaired (OR = 3.2, CI [1.57–6.51], p = 0.0007). The Benjamini–Hochberg false discovery rate for *DYM* was 0.04, and the heterogeneity p-value was 0.0026, suggesting that the over-transmission of the short-stature-associated allele was largely limited to patients with growth impairment. However, it should be noted that the most conservative Bonferroni correction of the two-sided heterogeneity p-value would result in loss of significance (p = 0.1664). Hence, it would be important to

Table 3 TDT of the CD-susceptibility and stature-associated alleles in growth impaired and nongrowth impaired CD patients

					Growth-impaired CD				Nongrowth-impaired CD				
Chr	Gene	CD/H[1]	SNP	Risk Allele[2]	T	U	OR [CI][3]	P-value	T	U	OR [CI][4]	P-value	Heterogeneity p-value[5]
18q21	*DYM*	H	rs8099594	G	32	10	3.20 [1.57–6.51]	**0.0007**	110	106	1.04 [0.79–1.36]	0.7855	**0.0026**
10q21.1	intergenic	CD	rs10761659	G	33	14	2.36 [1.26–4.41]	0.0056	119	90	1.32 [1.01–1.74]	0.0449	0.0942
2q37	*ATG16L1*	CD	rs10210302	T	27	11	2.45 [1.22–4.95]	0.0094	111	91	1.22 [0.92–1.61]	0.1594	0.0656
3p21	*BSN*	CD	rs9858542	A	31	15	2.07 [1.12–3.83]	0.0183	116	92	1.26 [0.96–1.66]	0.0961	0.1483
2q37	*ATG16L1*	CD	rs2241880	G	28	13	2.15 [1.12–4.16]	0.0192	118	93	1.27 [0.97–1.67]	0.0852	0.1426

Chr = chromosome, SNP = single nucleotide polymorphism, T = transmitted, U = untransmitted, OR = odds ratio, CI = confidence interval.

[1]CD = CD-risk SNP, H = stature-associated SNP.

[2]Risk allele refers to CD-risk allele for 10q21.1 intergenic region, *ATG16L1*, and *BSN*, and shorter height allele for *DYM*.

[3]OR reflects the odds of transmitting the risk allele to the growth-impaired CD patients.

[4]OR reflects the odds of transmitting the risk allele to the nongrowth impaired CD patients.

[5]Heterogeneity *P*-value reflects whether the OR are different for the growth-impaired and nongrowth impaired groups.

© 2010 The Authors
Annals of Human Genetics © 2010 Blackwell Publishing Ltd/University College London

validate our preliminary finding in another larger independent cohort.

The two CD-risk alleles, 10q21.1 intergenic region (rs10761659) and *ATG16L1* (rs10210302), were also shown to be over-transmitted in growth-impaired CD children (OR = 2.36, CI [1.26–4.41] p = 0.0056 and OR = 2.45, CI [1.22–4.95] p = 0.0094, respectively), but not those without growth impairment (OR = 1.32, CI [1.01–1.74] and OR = 1.22, CI [0.92–1.61], respectively). However, the false discovery rates for these SNPs were higher than *DYM*, 0.18 for rs10761659 and 0.20 for rs10210302, and the heterogeneity statistics on these SNPs were not significant; hence, a future study with a larger sample size will be needed to validate these findings. The previously reported SNPs in *OCTN1/2*, *IL6*, and the *TNF-α* promoter region that were implicated in linear growth in CD patients (Levine et al., 2005; Sawczenko et al., 2005; Russell et al., 2006) were not significantly associated with growth impairment in our cohort (Table S3).

Discussion

In this study, we found a 20.5% prevalence of growth impairment in the 317 CD children who comprised our cohort; this is similar to that reported over a decade ago from our institution using the same definition of growth impairment (Motil et al., 1993). The fact that there has been no significant change in the prevalence of growth impairment despite advances in therapy and nutrition suggests a genetic contribution to growth impairment in CD. Indeed, we observed over-transmission of the risk allele in a stature-related locus in the growth-impaired compared to the nongrowth-impaired CD children. Both the growth-impaired and nongrowth-impaired groups exhibited similar disease location and behavior, reducing disease severity as a major confounder. Despite the relatively small sample size, our cohort exhibited the previously confirmed CD-susceptibility variants selected for this analysis (Duerr et al., 2006; Wellcome Trust Case Control Consortium, 2007). This is the first study to report a possible association between a stature-related locus and growth impairment in children with CD. In addition, our data showed a trend for over-transmission of a risk allele from heterozygous parents to growth-impaired CD children for two known CD-susceptibility genes, 10q21.1 intergenic region and *ATG16L1*. These observations provide initial evidence for a genetic contribution to growth impairment in CD. Potentially, genetic influences due to a combination of CD-risk alleles and stature-associated loci that affect the general population may predispose CD patients to alterations in linear growth.

Stature is known to be strongly heritable, and twin and family studies have confirmed the role of genetics in up to 90% of the variation in height within populations (Preece, 1996; Silventoinen et al., 2003). Accordingly, subsequent studies have identified 47 genetic loci associated with stature in the general populations (Weedon et al., 2007; Lettre et al., 2008; Sanna et al., 2008; Weedon et al., 2008; Weedon & Frayling, 2008; Lettre, 2009). Many of these loci were also studied in our cohort, but only *DYM* was found to be significantly associated with growth impairment. This could be due to small sample size limiting our ability to detect associations, statistical fluctuation, including a "winner's curse" effect at *DYM*, or to a stronger effect of the *DYM* variant on growth impairment. Mutations in the *DYM* gene, which encodes dymeclin, have been linked to Dyggve–Melchior–Clausen syndrome and Smith–McCort dysplasia, rare autosomal-recessive skeletal dysplasias with and without mental retardation, respectively (El Ghouzzi et al., 2003; Neumann et al., 2006). The *DYM* mutations in Dyggve–Melchior–Clausen syndrome have been associated with loss of function, whereas those in Smith–McCort dysplasia have been mostly missense mutations. Despite *DYM*'s associations with these syndromes, only recently has its function become better characterized. The *DYM*-mutated murine model displays defects in endochondral bone formation. Available data also suggest that dymeclin participates in the traffic of proteins and vesicles into and out of the Golgi, which may play an important role in postnatal bone formation since transport defects could affect the synthesis, processing, secretion, or uptake of growth factors, and interactions with extracellular matrix (Osipovich et al., 2008). It has also been recently reported that dymeclin, widely expressed in primary chondrocytes and osteoblasts, is a peripheral, not transmembrane, protein of the Golgi apparatus (Dimitrov et al., 2009). Hence, compromised function of intracellular transport in the Golgi apparatus may serve as a mechanism underlying growth impairment in patients with CD. It should be noted that in our cohort the risk allele was found in both the heterozygous and homozygous state, but none of the patients had syndromic features of *DYM* mutations.

This is the largest study to date investigating CD-risk and stature-related loci associated with growth-impaired phenotype in pediatric CD. Prior smaller studies have reported an association of *OCTN1/2*, *IL6*, and *TNF-α* promoter polymorphisms with linear growth (Levine et al., 2005; Sawczenko et al., 2005; Russell et al., 2006). Two hundred children from the United Kingdom (UK) with CD were reported to have lower growth indices, including height, when they carried the TC haplotype of the *OCTN1/2* variant (Russell et al., 2006). Sawczenko et al. reported that 153 English and Swedish CD children with *IL6* GG genotype were shorter at diagnosis than those with GC or CC genotypes (Sawczenko et al., 2005). However, we were unable to replicate these findings in our US cohort, which may be due to different genetic

© 2010 The Authors
Annals of Human Genetics © 2010 Blackwell Publishing Ltd/University College London

pools studied and/or the different criteria selected for the growth-impaired phenotype. By contrast, genotyping of 87 Israeli CD patients revealed a correlation between presence of *TNF* 238 G/A polymorphism and increased height Z-scores, suggesting its protective effect on height retardation (Levine et al., 2005). Our data also demonstrated a similar trend on height of children carrying the same polymorphism (OR = 0.75), but this was not statistically significant. As reported by Wine et al., we also did not observe a correlation between the presence of *NOD2* polymorphisms and growth impairment (Wine et al., 2004). Our study suggests that linear growth in CD could be partially modulated by the interplay of various genetic variants, some of which may be at *DYM* and CD-risk alleles.

One of the limitations of our study is its small sample size, which could overestimate the effect of *DYM*. Since growth impairment occurs in 10–40% of CD patients, we will need a much larger cohort for the validation of transmission of risk alleles to growth-impaired children. Furthermore, it will be valuable to incorporate mid-parental heights into the calculation of height deficit, and to study the genetics of those who remain permanently growth impaired as adults. A very large multicenter study including a more comprehensive analysis of CD-risk alleles and stature-related alleles will likely further elucidate the contribution of genetics to growth impairment; such a study is in the planning phase.

In conclusion, our pilot study has identified a possible association between *DYM* and growth impairment in children with CD. Further studies to validate this association and to investigate other stature and CD-susceptibility variants are needed.

Acknowledgement

We thank the nurses and research staff of the Clinical and Translational Study Unit at Children's Hospital Boston for their assistance. We also thank Luçan Delemarre, Saum Ghodoussipour, Brian Harr, Marjan Kruijer, Marlous Moret, Sophie Allende-Richter, Dana Sandler, and Melissa Shuman who participated in data collection. This study would not have been possible without IBD patients and their families from Children's Hospital Boston and Children's Hospital of Wisconsin whom we thank for their participation. This research was supported by NIH General Clinical Research Center grant M01 RR02172 and NIH Harvard Clinical and Translational Science Center UL1 RR025758. JJL received support from the NIH training grant T32 DK 007477, Crohn's and Colitis Foundation of America Research Fellowship Award, and Children's Hospital Boston House Officer Development Award. JCE received support from the Ter Meulen Fund of the Royal Netherlands Academy of Arts and Sciences. We wish to acknowledge the insight of Dr. Kathleen J. Motil suggesting the potential genetic contribution to growth impairment in children with CD.

References

Barrett, J. C., Hansoul, S., Nicolae, D. L., Cho, J. H., Duerr, R. H., Rioux, J. D., Brant, S. R., Silverberg, M. S., Taylor, K. D., Barmada, M. M., Bitton, A., Dassopoulos, T., Datta, L. W., Green, T., Griffiths, A. M., Kistner, E. O., Murtha, M. T., Regueiro, M. D., Rotter, J. I., Schumm, L. P., Steinhart, A. H., Targan, S. R., Xavier, R. J., Libioulle, C., Sandor, C., Lathrop, M., Belaiche, J., Dewit, O., Gut, I., Heath, S., Laukens, D., Mni, M., Rutgeerts, P., Van Gossum, A., Zelenika, D., Franchimont, D., Hugot, J. P., De Vos, M., Vermeire, S., Louis, E., Cardon, L. R., Anderson, C. A., Drummond, H., Nimmo, E., Ahmad, T., Prescott, N. J., Onnie, C. M., Fisher, S. A., Marchini, J., Ghori, J., Bumpstead, S., Gwilliam, R., Tremelling, M., Deloukas, P., Mansfield, J., Jewell, D., Satsangi, J., Mathew, C. G., Parkes, M., Georges, M. & Daly, M. J. (2008) Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet* **40**, 955–962.

Benjamini, Y. & Hochberg, Y. (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc B* **57**, 289–300.

Borrelli, O., Bascietto, C., Viola, F., Bueno De Mesquita, M., Barbato, M., Mancini, V., Bosco, S. & Cucchiara, S. (2004) Infliximab heals intestinal inflammatory lesions and restores growth in children with Crohn's disease. *Dig Liver Dis* **36**, 342–347.

Browning, B. L., Huebner, C., Petermann, I., Gearry, R. B., Barclay, M. L., Shelling, A. N. & Ferguson, L. R. (2007) Has toll-like receptor 4 been prematurely dismissed as an inflammatory bowel disease gene? Association study combined with meta-analysis shows strong evidence for association. *Am J Gastroenterol* **102**, 2504–2512.

Dimitrov, A., Paupe, V., Gueudry, C., Sibarita, J. B., Raposo, G., Vielemeyer, O., Gilbert, T., Csaba, Z., Attie-Bitach, T., Cormier-Daire, V., Gressens, P., Rustin, P., Perez, F. & El Ghouzzi, V. (2009) The gene responsible for Dyggve-Melchior-Clausen syndrome encodes a novel peripheral membrane protein dynamically associated with the Golgi apparatus. *Hum Mol Genet* **18**, 440–453.

Duerr, R. H., Taylor, K. D., Brant, S. R., Rioux, J. D., Silverberg, M. S., Daly, M. J., Steinhart, A. H., Abraham, C., Regueiro, M., Griffiths, A., Dassopoulos, T., Bitton, A., Yang, H., Targan, S., Datta, L. W., Kistner, E. O., Schumm, L. P., Lee, A. T., Gregersen, P. K., Barmada, M. M., Rotter, J. I., Nicolae, D. L. & Cho, J. H. (2006) A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* **314**, 1461–1463.

El Ghouzzi, V., Dagoneau, N., Kinning, E., Thauvin-Robinet, C., Chemaitilly, W., Prost-Squarcioni, C., Al-Gazali, L. I., Verloes, A., Le Merrer, M., Munnich, A., Trembath, R. C. & Cormier-Daire, V. (2003) Mutations in a novel gene Dymeclin (FLJ20071) are responsible for Dyggve-Melchior-Clausen syndrome. *Hum Mol Genet* **12**, 357–364.

Essers, J. B., Lee, J. J., Kugathasan, S., Stevens, C. R., Grand, R. J. & Daly, M. J. (2009) Established genetic risk factors do not distinguish early and later onset Crohn's disease. *Inflamm Bowel Dis* **15**, 1508–1514.

Grandbastien, B., Peeters, M., Franchimont, D., Gower-Rousseau, C., Speckel, D., Rutgeerts, P., Belaiche, J., Cortot, A., Vlietinck, R. & Colombel, J. F. (1998) Anticipation in familial Crohn's disease. *Gut* **42**, 170–174.

Griffiths, A. M., Nguyen, P., Smith, C., Macmillan, J. H. & Sherman, P. M. (1993) Growth and clinical course of children with Crohn's disease. *Gut* **34**, 939–943.

© 2010 The Authors
Annals of Human Genetics © 2010 Blackwell Publishing Ltd/University College London

Hampe, J., Franke, A., Rosenstiel, P., Till, A., Teuber, M., Huse, K., Albrecht, M., Mayr, G., De La Vega, F. M., Briggs, J., Gunther, S., Prescott, N. J., Onnie, C. M., Hasler, R., Sipos, B., Folsch, U. R., Lengauer, T., Platzer, M., Mathew, C. G., Krawczak, M. & Schreiber, S. (2007) A genome-wide association scan of nonsynonymous SNPs identifies a susceptibility variant for Crohn disease in ATG16L1. *Nat Genet* **39**, 207–211.

Heyman, M. B., Garnett, E. A., Wojcicki, J., Gupta, N., Davis, C., Cohen, S. A., Gold, B. D., Kirschner, B. S., Baldassano, R. N., Ferry, G. D., Winter, H. S. & Kaplan, S. (2008) Growth hormone treatment for growth failure in pediatric patients with Crohn's disease. *J. Pediatr* **153**, 651–658.

Hildebrand, H., Karlberg, J. & Kristiansson, B. (1994) Longitudinal growth in children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* **18**, 165–173.

Hugot, J. P., Laurent-Puig, P., Gower-Rousseau, C., Olson, J. M., Lee, J. C., Beaugerie, L., Naom, I., Dupas, J. L., Van Gossum, A., Orholm, M., Bonaiti-Pellie, C., Weissenbach, J., Mathew, C. G., Lennard-Jones, J. E., Cortot, A., Colombel, J. F. & Thomas, G. (1996) Mapping of a susceptibility locus for Crohn's disease on chromosome 16. *Nature* **379**, 821–823.

Imielinski, M., Baldassano, R. N., Griffiths, A., Russell, R. K., Annese, V., Dubinsky, M., Kugathasan, S., Bradfield, J. P., Walters, T. D., Sleiman, P., Kim, C. E., Muise, A., Wang, K., Glessner, J. T., Saeed, S., Zhang, H., Frackelton, E. C., Hou, C., Flory, J. H., Otieno, G., Chiavacci, R. M., Grundmeier, R., Castro, M., Latiano, A., Dallapiccola, B., Stempak, J., Abrams, D. J., Taylor, K., Mcgovern, D., Silber, G., Wrobel, I., Quiros, A., Barrett, J. C., Hansoul, S., Nicolae, D. L., Cho, J. H., Duerr, R. H., Rioux, J. D., Brant, S. R., Silverberg, M. S., Taylor, K. D., Barmuda, M. M., Bitton, A., Dassopoulos, T., Datta, L. W., Green, T., Griffiths, A. M., Kistner, E. O., Murtha, M. T., Regueiro, M. D., Rotter, J. I., Schumm, L. P., Steinhart, A. H., Targan, S. R., Xavier, R. J., Libioulle, C., Sandor, C., Lathrop, M., Belaiche, J., Dewit, O., Gut, I., Heath, S., Laukens, D., Mni, M., Rutgeerts, P., Van Gossum, A., Zelenika, D., Franchimont, D., Hugot, J. P., De Vos, M., Vermeire, S., Louis, E., Cardon, L. R., Anderson, C. A., Drummond, H., Nimmo, E., Ahmad, T., Prescott, N. J., Onnie, C. M., Fisher, S. A., Marchini, J., Ghori, J., Bumpstead, S., Gwillam, R., Tremelling, M., Delukas, P., Mansfield, J., Jewell, D., Satsangi, J., Mathew, C. G., Parkes, M., Georges, M., Daly, M. J., Heyman, M. B., Ferry, G. D., Kirschner, B., Lee, J., Essers, J., Grand, R., Stephens, M., Levine, A., Piccoli, D., Van Limbergen, J., Cucchiara, S., Monos, D. S., Guthery, S. L., Denson, L., Wilson, D. C., Grant, S. F., Daly, M., Silverberg, M. S., Satsangi, J. & Hakonarson, H. (2009) Common variants at five new loci associated with early-onset inflammatory bowel disease. *Nat Genet* **41**, 1335–1340.

Kirschner, B. S. (1993) Permanent growth failure in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* **16**, 368–369.

Knight, C., El-Matary, W., Spray, C. & Sandhu, B. K. (2005) Long-term outcome of nutritional therapy in paediatric Crohn's disease. *Clin Nutr* **24**, 775–779.

Kugathasan, S., Baldassano, R. N., Bradfield, J. P., Sleiman, P. M., Imielinski, M., Guthery, S. L., Cucchiara, S., Kim, C. E., Frackelton, E. C., Annaiah, K., Glessner, J. T., Santa, E., Willson, T., Eckert, A. W., Bonkowski, E., Shaner, J. L., Smith, R. M., Otieno, F. G., Peterson, N., Abrams, D. J., Chiavacci, R. M., Grundmeier, R., Mamula, P., Tomer, G., Piccoli, D. A., Monos, D. S., Annese, V., Denson, L. A., Grant, S. F. & Hakonarson, H. (2008) Loci on 20q13 and 21q22 are associated with pediatric-onset inflammatory bowel disease. *Nat Genet* **40**, 1211–1215.

Lee, J. C., Bridger, S., Mcgregor, C., Macpherson, A. J. & Jones, J. E. (1999) Why children with inflammatory bowel disease are diagnosed at a younger age than their affected parent. *Gut* **44**, 808–811.

Lee, J. J., Escher, J. C., Shuman, M. J., Forbes, P. W., Delemarre, L. C., Harr, B. W., Kruijer, M., Moret, M., Allende-Richter, S. & Grand, R. J. (2010) Final adult height of children with inflammatory bowel disease is predicted by parental height and patient minimum height Z-score. *Inflamm Bowel Dis* [Epub ahead of print].

Lettre, G. (2009) Genetic regulation of adult stature. *Curr Opin Pediatr* **21**, 515–522.

Lettre, G., Jackson, A. U., Gieger, C., Schumacher, F. R., Berndt, S. I., Sanna, S., Eyheramendy, S., Voight, B. F., Butler, J. L., Guiducci, C., Illig, T., Hackett, R., Heid, I. M., Jacobs, K. B., Lyssenko, V., Uda, M., Boehnke, M., Chanock, S. J., Groop, L. C., Hu, F. B., Isomaa, B., Kraft, P., Peltonen, L., Salomaa, V., Schlessinger, D., Hunter, D. J., Hayes, R. B., Abecasis, G. R., Wichmann, H. E., Mohlke, K. L. & Hirschhorn, J. N. (2008) Identification of ten loci associated with height highlights new biological pathways in human growth. *Nat Genet* **40**, 584–591.

Levine, A., Shamir, R., Wine, E., Weiss, B., Karban, A., Shaoul, R. R., Reif, S. S., Yakir, B., Friedlander, M., Kaniel, Y. & Leshinsky-Silver, E. (2005) TNF promoter polymorphisms and modulation of growth retardation and disease severity in pediatric Crohn's disease. *Am J Gastroenterol* **100**, 1598–1604.

Libioulle, C., Louis, E., Hansoul, S., Sandor, C., Farnir, F., Franchimont, D., Vermeire, S., Dewit, O., De Vos, M., Dixon, A., Demarche, B., Gut, I., Heath, S., Foglio, M., Liang, L., Laukens, D., Mni, M., Zelenika, D., Van Gossum, A., Rutgeerts, P., Belaiche, J., Lathrop, M. & Georges, M. (2007) Novel Crohn disease locus identified by genome-wide association maps to a gene desert on 5p13.1 and modulates expression of PTGER4. *PLoS Genet* **3**, e58.

Markowitz, J. & Daum, F. (1994) Growth impairment in pediatric inflammatory bowel disease. *Am J Gastroenterol* **89**, 319–326.

Motil, K. J., Grand, R. J., Davis-Kraft, L., Ferlic, L. L. & Smith, E. O. (1993) Growth failure in children with inflammatory bowel disease: a prospective study. *Gastroenterology* **105**, 681–691.

Neumann, L. M., El Ghouzzi, V., Paupe, V., Weber, H. P., Fastnacht, E., Leenen, A., Lyding, S., Klusmann, A., Mayatepek, E., Pelz, J. & Cormier-Daire, V. (2006) Dyggve-Melchior-Clausen syndrome and Smith-McCort dysplasia: clinical and molecular findings in three families supporting genetic heterogeneity in Smith-McCort dysplasia. *Am J Med Genet A* **140**, 421–426.

Osipovich, A. B., Jennings, J. L., Lin, Q., Link, A. J. & Ruley, H. E. (2008) Dyggve-Melchior-Clausen syndrome: chondrodysplasia resulting from defects in intracellular vesicle traffic. *Proc Natl Acad Sci USA* **105**, 16171–16176.

Parkes, M., Barrett, J. C., Prescott, N. J., Tremelling, M., Anderson, C. A., Fisher, S. A., Roberts, R. G., Nimmo, E. R., Cummings, F. R., Soars, D., Drummond, H., Lees, C. W., Khawaja, S. A., Bagnall, R., Burke, D. A., Todhunter, C. E., Ahmad, T., Onnie, C. M., Mcardle, W., Strachan, D., Bethel, G., Bryan, C., Lewis, C. M., Deloukas, P., Forbes, A., Sanderson, J., Jewell, D. P., Satsangi, J., Mansfield, J. C., Cardon, L. & Mathew, C. G. (2007) Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn's disease susceptibility. *Nat Genet* **39**, 830–832.

© 2010 The Authors
Annals of Human Genetics © 2010 Blackwell Publishing Ltd/University College London

Peltekova, V. D., Wintle, R. F., Rubin, L. A., Amos, C. I., Huang, Q., Gu, X., Newman, B., Van Oene, M., Cescon, D., Greenberg, G., Griffiths, A. M., St George-Hyslop, P. H. & Siminovitch, K. A. (2004) Functional variants of OCTN cation transporter genes are associated with Crohn disease. *Nat Genet* **36**, 471–475.

Pfefferkorn, M., Burke, G., Griffiths, A., Markowitz, J., Rosh, J., Mack, D., Otley, A., Kugathasan, S., Evans, J., Bousvaros, A., Moyer, M. S., Wyllie, R., Oliva-Hemker, M., Carvalho, R., Crandall, W., Keljo, D., Walters, T. D., Leleiko, N. & Hyams, J. (2009) Growth abnormalities persist in newly diagnosed children with Crohn disease despite current treatment paradigms. *J Pediatr. Gastroenterol Nutr* **48**, 168–174.

Polito, J. M., 2nd, Rees, R. C., Childs, B., Mendeloff, A. I., Harris, M. L. & Bayless, T. M. (1996) Preliminary evidence for genetic anticipation in Crohn's disease. *Lancet* **347**, 798–800.

Potocnik, U., Ferkolj, I., Glavac, D. & Dean, M. (2004) Polymorphisms in multidrug resistance 1 (MDR1) gene are associated with refractory Crohn disease and ulcerative colitis. *Genes Immun* **5**, 530–539.

Preece, M. A. (1996) The genetic contribution to stature. *Horm Res* **45**(Suppl 2), 56–58.

Prescott, N. J., Fisher, S. A., Franke, A., Hampe, J., Onnie, C. M., Soars, D., Bagnall, R., Mirza, M. M., Sanderson, J., Forbes, A., Mansfield, J. C., Lewis, C. M., Schreiber, S. & Mathew, C. G. (2007) A nonsynonymous SNP in ATG16L1 predisposes to ileal Crohn's disease and is independent of CARD15 and IBD5. *Gastroenterology* **132**, 1665–1671.

Puntis, J., Mcneish, A. S. & Allan, R. N. (1984) Long term prognosis of Crohn's disease with onset in childhood and adolescence. *Gut* **25**, 329–336.

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A., Bender, D., Maller, J., Sklar, P., De Bakker, P. I., Daly, M. J. & Sham, P. C. (2007) PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* **81**, 559–575.

Rioux, J. D., Daly, M. J., Silverberg, M. S., Lindblad, K., Steinhart, H., Cohen, Z., Delmonte, T., Kocher, K., Miller, K., Guschwan, S., Kulbokas, E. J., O'leary, S., Winchester, E., Dewar, K., Green, T., Stone, V., Chow, C., Cohen, A., Langelier, D., Lapointe, G., Gaudet, D., Faith, J., Branco, N., Bull, S. B., Mcleod, R. S., Griffiths, A. M., Bitton, A., Greenberg, G. R., Lander, E. S., Siminovitch, K. A. & Hudson, T. J. (2001) Genetic variation in the 5q31 cytokine gene cluster confers susceptibility to Crohn disease. *Nat Genet* **29**, 223–228.

Rioux, J. D., Silverberg, M. S., Daly, M. J., Steinhart, A. H., Mcleod, R. S., Griffiths, A. M., Green, T., Brettin, T. S., Stone, V., Bull, S. B., Bitton, A., Williams, C. N., Greenberg, G. R., Cohen, Z., Lander, E. S., Hudson, T. J. & Siminovitch, K. A. (2000) Genomewide search in Canadian families with inflammatory bowel disease reveals two novel susceptibility loci. *Am J Hum Genet* **66**, 1863–1870.

Rioux, J. D., Xavier, R. J., Taylor, K. D., Silverberg, M. S., Goyette, P., Huett, A., Green, T., Kuballa, P., Barmada, M. M., Datta, L. W., Shugart, Y. Y., Griffiths, A. M., Targan, S. R., Ippoliti, A. F., Bernard, E. J., Mei, L., Nicolae, D. L., Regueiro, M., Schumm, L. P., Steinhart, A. H., Rotter, J. I., Duerr, R. H., Cho, J. H., Daly, M. J. & Brant, S. R. (2007) Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. *Nat Genet* **39**, 596–604.

Russell, R. K., Drummond, H. E., Nimmo, E. E., Anderson, N., Smith, L., Wilson, D. C., Gillett, P. M., Mcgrogan, P., Hassan, K., Weaver, L. T., Bisset, M., Mahdi, G. & Satsangi, J. (2005) Genotype-phenotype analysis in childhood-onset Crohn's disease: NOD2/CARD15 variants consistently predict phenotypic characteristics of severe disease. *Inflamm. Bowel Dis* **11**, 955–964.

Russell, R. K., Drummond, H. E., Nimmo, E. R., Anderson, N. H., Noble, C. L., Wilson, D. C., Gillett, P. M., Mcgrogan, P., Hassan, K., Weaver, L. T., Bisset, W. M., Mahdi, G. & Satsangi, J. (2006) Analysis of the influence of OCTN1/2 variants within the IBD5 locus on disease susceptibility and growth indices in early onset inflammatory bowel disease. *Gut* **55**, 1114–1123.

Sanna, S., Jackson, A. U., Nagaraja, R., Willer, C. J., Chen, W. M., Bonnycastle, L. L., Shen, H., Timpson, N., Lettre, G., Usala, G., Chines, P. S., Stringham, H. M., Scott, L. J., Dei, M., Lai, S., Albai, G., Crisponi, L., Naitza, S., Doheny, K. F., Pugh, E. W., Ben-Shlomo, Y., Ebrahim, S., Lawlor, D. A., Bergman, R. N., Watanabe, R. M., Uda, M., Tuomilehto, J., Coresh, J., Hirschhorn, J. N., Shuldiner, A. R., Schlessinger, D., Collins, F. S., Davey Smith, G., Boerwinkle, E., Cao, A., Boehnke, M., Abecasis, G. R. & Mohlke, K. L. (2008) Common variants in the GDF5-UQCC region are associated with variation in human height. *Nat Genet* **40**, 198–203.

Sawczenko, A., Azooz, O., Paraszczuk, J., Idestrom, M., Croft, N. M., Savage, M. O., Ballinger, A. B. & Sanderson, I. R. (2005) Intestinal inflammation-induced growth retardation acts through IL-6 in rats and depends on the -174 IL-6 G/C polymorphism in children. *Proc Natl Acad Sci USA* **102**, 13260–13265.

Silventoinen, K., Sammalisto, S., Perola, M., Boomsma, D. I., Cornes, B. K., Davis, C., Dunkel, L., De Lange, M., Harris, J. R., Hjelmborg, J. V., Luciano, M., Martin, N. G., Mortensen, J., Nistico, L., Pedersen, N. L., Skytthe, A., Spector, T. D., Stazi, M. A., Willemsen, G. & Kaprio, J. (2003) Heritability of adult body height: a comparative study of twin cohorts in eight countries. *Twin Res* **6**, 399–408.

Silverberg, M. S., Satsangi, J., Ahmad, T., Arnott, I. D., Bernstein, C. N., Brant, S. R., Caprilli, R., Colombel, J. F., Gasche, C., Geboes, K., Jewell, D. P., Karban, A., Loftus, E. V., Jr, Pena, A. S., Riddell, R. H., Sachar, D. B., Schreiber, S., Steinhart, A. H., Targan, S. R., Vermeire, S. & Warren, B. F. (2005) Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* **19**(Suppl A), 5–36.

Stoll, M., Corneliussen, B., Costello, C. M., Waetzig, G. H., Mellgard, B., Koch, W. A., Rosenstiel, P., Albrecht, M., Croucher, P. J., Seegert, D., Nikolaus, S., Hampe, J., Lengauer, T., Pierrou, S., Foelsch, U. R., Mathew, C. G., Lagerstrom-Fermer, M. & Schreiber, S. (2004) Genetic variation in DLG5 is associated with inflammatory bowel disease. *Nat Genet* **36**, 476–480.

Tysk, C., Lindberg, E., Jarnerot, G. & Floderus-Myrhed, B. (1988) Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking. *Gut* **29**, 990–996.

Van Limbergen, J., Russell, R. K., Drummond, H. E., Aldhous, M. C., Round, N. K., Nimmo, E. R., Smith, L., Gillett, P. M., Mcgrogan, P., Weaver, L. T., Bisset, W. M., Mahdi, G., Arnott, I. D., Satsangi, J. & Wilson, D. C. (2008) Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* **135**, 1114–1122.

Walters, T. D., Gilman, A. R. & Griffiths, A. M. (2007) Linear growth improves during infliximab therapy in children with chronically active severe Crohn's disease. *Inflamm Bowel Dis* **13**, 424–430.

© 2010 The Authors
Annals of Human Genetics © 2010 Blackwell Publishing Ltd/University College London

Weedon, M. N. & Frayling, T. M. (2008) Reaching new heights: insights into the genetics of human stature. *Trends Genet* **24**, 595–603.

Weedon, M. N., Lango, H., Lindgren, C. M., Wallace, C., Evans, D. M., Mangino, M., Freathy, R. M., Perry, J. R., Stevens, S., Hall, A. S., Samani, N. J., Shields, B., Prokopenko, I., Farrall, M., Dominiczak, A., Johnson, T., Bergmann, S., Beckmann, J. S., Vollenweider, P., Waterworth, D. M., Mooser, V., Palmer, C. N., Morris, A. D., Ouwehand, W. H., Zhao, J. H., Li, S., Loos, R. J., Barroso, I., Deloukas, P., Sandhu, M. S., Wheeler, E., Soranzo, N., Inouye, M., Wareham, N. J., Caulfield, M., Munroe, P. B., Hattersley, A. T., Mccarthy, M. I. & Frayling, T. M. (2008) Genome-wide association analysis identifies 20 loci that influence adult height. *Nat. Genet* **40**, 575–583.

Weedon, M. N., Lettre, G., Freathy, R. M., Lindgren, C. M., Voight, B. F., Perry, J. R., Elliott, K. S., Hackett, R., Guiducci, C., Shields, B., Zeggini, E., Lango, H., Lyssenko, V., Timpson, N. J., Burtt, N. P., Rayner, N. W., Saxena, R., Ardlie, K., Tobias, J. H., Ness, A. R., Ring, S. M., Palmer, C. N., Morris, A. D., Peltonen, L., Salomaa, V., Davey Smith, G., Groop, L. C., Hattersley, A. T., Mccarthy, M. I., Hirschhorn, J. N. & Frayling, T. M. (2007) A common variant of HMGA2 is associated with adult and childhood height in the general population. *Nat. Genet* **39**, 1245–1250.

Wellcome Trust Case Control Consortium. (2007) Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**, 661–678.

Wine, E., Reif, S. S., Leshinsky-Silver, E., Weiss, B., Shaoul, R. R., Shamir, R., Wasserman, D., Lerner, A., Boaz, M. & Levine, A. (2004) Pediatric Crohn's disease and growth retardation: the role of genotype, phenotype, and disease severity. *Pediatrics* **114**, 1281–1286.

Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1: Complete list of SNPs genotyped
Table S2: Montreal Classification based on growth status
Table S3: TDT reveals no statistical relationship between loci shown and linear growth in CD

As a service to our authors and readers, this journal provides supporting information supplied by the authors. Such materials are peer-reviewed and may be re-organised for online delivery, but are not copy-edited or typeset. Technical support issues arising from supporting information (other than missing files) should be addressed to the authors.

Received: 6 March 2010
Accepted: 17 July 2010

© 2010 The Authors
Annals of Human Genetics © 2010 Blackwell Publishing Ltd/University College London