Brief Report

Common Variation in the *LMNA* Gene (Encoding Lamin A/C) and Type 2 Diabetes

Association Analyses in 9,518 Subjects

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Mutations in the *LMNA* gene (encoding lamin A/C) underlie familial partial lipodystrophy, a syndrome of monogenic insulin resistance and diabetes. *LMNA* maps to the well-replicated diabetes-linkage region on chromosome 1q, and there are reported associations between *LMNA* single nucleotide polymorphisms (SNPs) (particularly rs4641; H566H) and metabolic syndrome components. We examined the relationship between *LMNA* variation and type 2 diabetes (using six tag SNPs capturing >90% of common variation) in several large datasets. Analysis of 2,490 U.K. diabetic case and 2,556 control subjects revealed no significant associations at either genotype or haplotype level: the minor allele at rs4641 was no more frequent in case subjects (allelic odds ratio [OR] 1.07 [95% CI 0.98–1.17], *P* = 0.15). In 390 U.K. trios, family-based association analyses revealed nominally significant overtransmission of the major allele at rs12063564 (*P* = 0.01), which was not corroborated in other samples. Finally, genotypes for 2,817 additional subjects from the International 1q Consortium revealed no consistent case-control or family-based associations with *LMNA* variants. Across all our data, the OR for the rs4641 minor allele approached but did not attain significance (1.07 [0.99–1.15], *P* = 0.08). Our data do not therefore support a major effect of *LMNA* variation on diabetes risk. However, in a meta-analysis including other available data, there is evidence that rs4641 has a modest effect on diabetes susceptibility (1.10 [1.04–1.16], *P* = 0.001). *Diabetes* 56:879–883, 2007

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*A complete list of the International Type 2 Diabetes 1q Consortium is available in the online appendix.

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FPLD, familial partial lipodystrophy; HRC, Human Random Control; MAF, minor allele frequency; SNP, single nucleotide polymorphism.

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See accompanying Brief Reports, p. 694 and 884.

Only a limited number of genes with reproducible evidence of association with type 2 diabetes have been described. One emerging theme is the frequency with which rare mutations in these same genes display causal involvement in monogenic forms of diabetes or insulin resistance (1). Consequently, there are good grounds for considering genes causing monogenic forms of disease as especially promising candidates with regard to susceptibility to common forms of type 2 diabetes.

Mutations in the *LMNA* gene cause one form of familial partial lipodystrophy (FPLD) (2), a monogenic syndrome of extreme insulin resistance characterized by abnormal fat distribution, dyslipidemia, hypertension, hepatic steatosis, and diabetes. *LMNA* codes (by alternate splicing) for two major protein products, lamin A and C. As constituents of the nuclear envelope, these have both structural and regulatory functions (3). *LMNA* mutations (at sites other than those underlying FPLD) are responsible for a range of pathologies (the "laminopathies") affecting multiple cell types (4). The structure-function relationships underlying these diverse phenotypes are unclear. Equally, the mechanisms whereby *LMNA* mutations lead to FPLD are not understood, though loss of *LMNA* binding to the sterol responsive element binding protein 1 may explain the disturbed adipocyte differentiation and development (5). Consequent diversion of dietary-derived triglycerides into ectopic sites (liver and skeletal muscle) likely underlies the profound insulin resistance. Similar mechanisms

TABLE 1
Characteristics of the U.K. subjects studied

	Case samples			Control samples	
	Probands from sibpair families	Warren2 case subjects	Probands from parent-offspring trios*	1958 Birth Cohort	HRC resource
n	571	1,569	390	2,017	539
Male (%)	54.4	59.9	59.4	50.1	49.4
Age at examination (years)	64.1 ± 8.1	60.2 ± 8.2	46.3 ± 7.1	Not available	Not known
Age at diagnosis (years)	55.3 ± 8.4	51.4 ± 7.5	40.3 ± 7.7	Not applicable	Not applicable
BMI (kg/m^2)	28.4 (24.0–33.7)	31.5 (26.1–37.9)	32.3 (26.2–39.8)	Not available	Not known
Waist-to-hip ratio (males)	0.95 (0.89–1.03)	0.98 (0.92–1.06)	0.98 (0.91–1.05)	Not available	Not known
Waist-to-hip ratio (females)	0.87 (0.80–0.93)	0.91 (0.84–0.98)	0.89 (0.81–0.98)	Not available	Not known
Treatment (ins/OHA/diet)† (%)	16/69/15	8/62/31	18/63/19	Not applicable	Not applicable

Data are mean ± SD or geometric mean (SD range). *Results given for all trios probands (n = 390). Of these, 350 were of British/Irish origin (60% male; age at diagnosis 40.3 ± 7.4 years; BMI 32.3 kg/m^2 [28.4–37.3]). †Treatment at the time of ascertainment. ins, insulin; OHA, oral hypoglycemic agent.

are increasingly implicated in the pathogenesis of insulin resistance, which characterizes type 2 diabetes (6).

LMNA's credentials as a type 2 diabetes candidate are enhanced by prior genetic data. *LMNA* maps within the well-replicated area of type 2 diabetes linkage on chromosome 1q21–24, which has generated powerful signals in European, East-Asian, and Native-American pedigrees (7,8). Additionally, there have been several recent association studies, most concentrating on a coding variant in exon 10 (rs4641; H566H). As this codon is directly adjacent to the lamin A/C alternate splice site, even synonymous DNA sequence variation has the potential to modulate relative expression of *LMNA* products.

Initial reports in indigenous North American populations (9,10) suggested the minor allele of rs4641 was associated with increased BMI and central obesity. However, the largest published study of this variant (11) (1,338 Pima Indians, 60% with diabetes) detected no association with diabetes, BMI, lipid parameters, insulin sensitivity, or β-cell function. Subsequent data from the same group indicated a possible association with abdominal adipocyte size (12). Likewise, a small Japanese study found no association between rs4641 and diabetes (13). A more extensive survey of common variation within *LMNA* (six tag single nucleotide polymorphisms [SNPs] including rs4641) in the Amish Family Study (n = 971, 10% with type 2 diabetes) reported that rs4641 was associated with metabolic syndrome and triglyceride levels but not diabetes (14).

Most recently, analyses of appropriately large Danish samples (15) have provided the most convincing evidence yet that the minor allele at rs4641 is associated with type 2 diabetes and that other *LMNA* variants show (at least nominally) significant associations with metabolic and anthropometric traits. The present study sought to examine these interesting, but inconsistent, findings with respect to type 2 diabetes susceptibility in analyses of 6,701 U.K. subjects and, through the International 1q Consortium, a further 2,817 samples from populations with the strongest evidence of linkage to the *LMNA* region.

First, we performed a large-scale case-control analysis in 5,046 U.K. samples (Table 1). We included as case subjects 571 probands, all ascertained for positive family history, from the Diabetes U.K. Warren 2 sibpair collection; 1,569 type 2 diabetic subjects from the MRC/Diabetes U.K. case resource, ascertained for type 2 diabetes diagnosed before age 65 years; and 350 exclusively British/Irish probands from the Warren 2 trios resource. As control subjects, we examined 539 U.K. subjects (Human Random Control [HRC]+), 472 from the HRC resource plus 67 non-HRC samples from the same source (ECACC, Salisbury, U.K.), and 2,017 from the British Birth Cohort of 1958. All cases were diagnosed with diabetes based on biochemical evidence of hyperglycemia and/or requirement for oral agents or insulin. Subtypes other than type 2 diabetes were excluded using clinical, genetic, and immunological criteria (all are GAD antibody negative). Glucose tolerance status is not known for any of the control subjects. All subjects were unrelated and of British/Irish-European origin. Further details of ascertainment, subject characteristics, and validation of these samples are provided in the online appendix (available at http://dx.doi.org/10.2337/db06-0930).

Using pairwise tag selection approaches (16) applied to U.K. control genotype data for *LMNA*-region SNPs (minor allele frequency [MAF] >1%) generated by the 1q Consortium (see below), we prioritized six tag SNPs (threshold $r^2 > 0.8$) for genotyping. Three mapped upstream of the *LMNA* coding region (rs12063564 [MAF 0.15], rs6661281 [MAF 0.39], and rs955383 [MAF 0.24]), one in the large first intron (rs693671 [MAF 0.04]), and two were synonymous SNPs (rs505058 [D446D] in exon 7 [MAF 0.06] and rs4641 [H566H] in exon 10 [MAF 0.30]). rs12063564 was included as a proxy for a 1q Consortium SNP (rs4661146), which failed assay redesign (mutual r^2 of one in the CEU component of HapMap). SNP positions and linkage disequilibrium relationships are summarized in online appendix Figure A. Using HapMap phase 2 data where available (rs12063564, rs6661281, and rs955383) plus HapMap proxies for rs693671 and rs505058 (identified using the 1q Consortium genotypes), we estimate that these SNPs capture >90% of common variation at an $r^2 > 0.8$ across the 83-kb region (containing 43 HapMap SNPs), which spans *LMNA* and its putative regulatory regions.

TABLE 2
Case-control analysis of combined groups

SNP	NCBI build 36 position	Genotype	Combined case subjects W2SP + W2C (n = 2,140)	W2TP (n = 350)	Combined control subjects (n = 2,556)	Case-control: W2SP + W2C vs. controls		Case-control: including W2TP	
						Cochran Armitage test	Recessive test*	Cochran Armitage test	Recessive test*
		TT	1,435 (70.8)	240 (74.5)	1,745 (72.6)				
		TC	530 (26.1)	77 (23.9)	614 (25.6)				
rs12063564	154321809	CC	63 (3.1)	5 (1.6)	43 (1.8)	0.039	0.16	0.098	0.30
		TT	740 (36.1)	117 (36.4)	843 (34.4)				
		TC	941 (45.9)	153 (47.7)	1,224 (49.9)				
rs6661281	154341469	CC	371 (18.1)	51 (15.9)	386 (15.7)	0.76	—	0.89	—
		AA	1,188 (57.5)	174 (54.7)	1,344 (55.5)				
		AG	751 (36.4)	116 (36.5)	924 (38.2)				
rs955383	154348654	GG	126 (6.1)	28 (8.8)	153 (6.3)	0.23	—	0.41	—
		TT	1,889 (91.5)	274 (87.5)	2,296 (91.7)				
		TC	168 (8.1)	37 (11.8)	205 (8.2)				
rs693671	154359819	CC	7 (0.3)	2 (0.6)	3 (0.1)	0.68	0.83	0.26	0.39
		TT	1,814 (87.3)	272 (84.7)	2,110 (87.8)				
		TC	250 (12.0)	47 (14.6)	287 (11.9)				
rs505058	154372809	CC	14 (0.7)	2 (0.6)	6 (0.2)	0.39	0.60	0.22	0.37
		CC	1,072 (51.6)	157 (50.0)	1,316 (53.8)				
		CT	851 (40.9)	132 (42.0)	948 (38.8)				
rs4641	154374158	TT	156 (7.5)	25 (8.0)	181 (7.4)	0.21	—	0.15	—

Data are n (%). *Recessive test used where MAF was <20%; considers common allele as recessive. NCBI, National Center for Biotechnology Information; W2C, Warren2 case subjects; W2SP, Warren2 sibpair probands; W2TP, Warren2 trio probands.

Genotyping was performed at KBiosciences (Hoddesdon, U.K.) using a fluorescence-based competitive allele-specific (KASPar) assay (details available from the authors upon request). Call rates for all SNPs exceeded 95% overall (with no SNP in any sample <90%). Genotyping performance was evaluated against stringent quality control criteria, including a discrepancy rate on duplicate genotyping <0.5%; there were no Mendelian inconsistencies observed in 963 families and no departure from Hardy-Weinberg equilibrium (all $P > 0.05$) in control subjects.

Genotype counts by subgroup are shown in online appendix Table B. In the absence of heterogeneity between case and control subgroups ($P > 0.01$), our primary analyses used pooled case and control data. Analyses were conducted with both inclusion (to maximize power) and exclusion (to preserve the independence of the family-based analyses) of the 350 British/Irish Warren 2 trio probands. Genotype frequency comparisons were implemented in StatXact 6 (Cytel Corporation, Cambridge, MA) using the Cochran-Armitage trend test (additive model) supplemented by recessive analyses where the MAF was <20%.

In the case-control study (Table 2), only a single SNP, rs12063564, displayed nominal evidence (uncorrected $P <$ 0.05) of association with type 2 diabetes (odds ratio [OR] per additional copy of allele C: 1.13 [95% CI 1.01–1.27], Cochran-Armitage test, $P = 0.039$). However, inclusion of the Warren 2 trio probands rendered this association nonsignificant ($P = 0.098$). Notably, the minor allele of rs4641 showed no significant association with type 2 diabetes (all case vs. all control subjects: 1.07 [0.98–1.17], $P = 0.15$). Stratification by sex did not alter the findings for any SNP.

LMNA haplotypes were inferred using the expectation-maximization algorithm implemented in HelixTree (Bozeman, MT) (online appendix Table C). Haplotype trend regression (17) revealed no evidence for haplotypic associations ($P = 0.20$).

Family-based association tests (Table 3) were performed in all 1,170 members of the full set of 390 parent-offspring trio pedigrees (see online appendix). The transmission disequilibrium test, implemented in UNPHASED (18), indicated overtransmission of the common allele (T) at rs12063564 ($P = 0.01$) but no evidence of departure from expectation for any other allele or haplotype. Estimates of overall significance (i.e., global tests of whether any of the individual SNPs or haplotypes showed transmission disequilibrium, based on 10,000 permutations) were not significant for either single-point ($P =$ 0.054) or haplotypic (0.74) analyses.

Using *LMNA* genotypes from all 1,406 members of the 573 Warren 2 sibpair families, there was no indication that

TABLE 3
Family-based association in 390 U.K. trios

	rs12063564	rs6661281	rs955383	rs693671	rs505058	rs4641
Minor allele	C	C	G	C	C	T
T/NT*	63/95	148/149	127/117	36/37	41/48	129/119
P	0.01	0.95	0.52	0.91	0.46	0.52

Analyses are by single-point transmission disequilibrium test. The global P value ($P = 0.054$) addresses the null hypothesis that there is no departure from expectation across the set of six single-point tests. *Transmission/nontransmission (T/NT) of minor allele to offspring. Permutation $P = 0.054$.

common variants were contributing to the 1q linkage signal previously observed in these pedigrees ($P > 0.8$, using the program LAMP, which tests the extent to which associated SNPs can account for regional linkage [19]). In addition, using ANOVA approaches (SPSS version 14) in the case samples, we found no evidence that *LMNA* SNPs were associated with age of diagnosis of diabetes, BMI, or waist-to-hip ratio, after logarithmic transformation to normality where appropriate (see online appendix Table D for rs4641 data; other data not shown).

Next, genotype data gathered by the International Type 2 Diabetes 1q Consortium (see online appendix), in the course of efforts to map susceptibility variants within the replicated linkage region on chromosome 1q, allowed us to extend our *LMNA* analysis in 3,707 samples from the 1q case-control study (2,084 non-U.K.; 890 U.K.) and Pima family study ($n = 733$). The 1q Consortium has to date attempted genotyping of 20 SNPs (online appendix Figure A and Table E) spanning the *LMNA* region in these samples. The 1q case-control study includes some of the U.K. samples included in the analyses described above (Warren 2 sibpair probands and HRC+: these were the only U.K. samples typed for more than the six tag SNPs) and Amish and Pima samples included in previous publications (11,14). Genotypes were gathered as part of three 1536-plex Illumina Golden Gate bundles (20). Single-point (Cochran-Armitage test using Stata version 8) and haplotype-based (haplotype trend regression using HelixTree) analyses of these data revealed no consistent associations between *LMNA* SNPs and type 2 diabetes (data not shown). Analyses of the tag SNPs typed in the 1q Consortium samples (rs6661281, rs955383, rs693671, rs505058, rs4641, and rs4661146) confirmed no association with type 2 diabetes in the Amish, Pima, U.K., Shanghai, or Hong Kong case-control datasets. Nominal associations for rs6661281 in the Utah sample ($P = 0.015$), and for rs693671 ($P = 0.003$) and rs505058 ($P = 0.002$) in the French (additive model), were not substantiated in other samples. Combined analysis of information from all seven datasets (using the Mantel-Haenszel meta-analysis method under recessive, dominant, and additive models) showed no convincing association of *LMNA* tag SNPs with type 2 diabetes (online appendix Table F). Notably, rs4641 was not associated with type 2 diabetes in any of the samples (online appendix Table G).

Finally, a further 733 Pima samples from the original linkage pedigrees (21 and online appendix data) were, with 99 individuals from the case-control sample, analyzed using family-based association methods. These 832 Pima samples included 570 type 2 diabetic subjects (diagnosed <45 years), 104 nondiabetic siblings (aged >45 years), and 158 parents (to reconstruct family relationships). Family-based association analyses under the additive model were performed using binomial generalized estimating equations to control for family membership (22). Again, no *LMNA* SNPs were associated with type 2 diabetes (all $P > 0.3$).

For reasons stated earlier, *LMNA* is a logical choice of candidate to investigate for association with multifactorial type 2 diabetes. In this study, we have been unable to show any compelling evidence of association with any of the SNPs typed. It is noteworthy that the nominally significant results at rs12063564 in the case-control and family-based analyses lie in the opposite direction. The estimate of the combined OR (including all the nonoverlapping data reported in the present study), was calculated using the inverse variance method (23) to allow proper adjustment for nonindependence in some of the datasets (e.g., Amish). In this meta-analysis, the effect of rs4641 on diabetes risk approached but did not attain nominal significance: allelic OR 1.07 (95% CI 0.99–1.15), $P = 0.08$.

The strongest evidence supporting an association between the minor allele of rs4641 and type 2 diabetes risk comes from a large study of Danish subjects (15). In comparison of 1,324 case and 4,386 control subjects, the observed OR was 1.14 (95% CI 1.03–1.26). While our study fails to replicate this association, the OR estimates from the two studies show substantial overlap in their CIs. Ascertainment effects, as well as sampling error, may have contributed to modest differences in the effect size estimates. Many of the U.K. case subjects were selected for positive family history and/or early disease onset, maneuvers expected to boost effect size estimates compared with the less-selective Danish case ascertainment. However, differences in control ascertainment may have had a small effect in the opposite direction. The Danish control subjects are confirmed as normoglycemic, while glycemic status is unknown for the U.K. control subjects. However, given the relatively low prevalence of diabetes in middle-aged U.K. subjects (24), the magnitude of the dilution of effect size engendered by such misclassification can be shown to be extremely modest (25).

Meta-analysis provides one route to improved specification of true effect sizes. Combining all the case-control data in the present study with the previous Japanese report (13) (using inverse variance method, not including the previous Amish and Pima data, given overlap with the current study), the per-allele OR for the minor allele at rs4641 reaches 1.08 (95% CI 1.01–1.16), $P = 0.04$. Further, if the Danish case-control data (15) are included (contributing 42% of the total 13,694 genotypes), the evidence in favor of a type 2 diabetes susceptibility effect at rs4641 increases substantially (1.10 [1.04–1.16], $P = 0.001$). While our data cannot be considered to provide replication ($P < 0.05$) of the association reported by Wegner et al. (15), the fact that this combined analysis generates a more significant result than that seen in either study alone indicates that the U.K. data provides some support for the Danish findings, particularly when one factors in the strong biological candidacy of *LMNA*.

These data again illustrate the tremendous difficulties that exist in the detection, replication, and interpretation of association analyses for variants with modest susceptibility effects. If the true effect size of rs4641 is an OR of 1.1, then even a study of 2,500 case-control pairs has only 57% power (given a liberal $\alpha = 0.05$). Indeed, reaching stringent genome-wide significance ($P = 5 \times 10^{-8}$) for such a variant would require analysis of >25,000 case-control pairs. In addition, such modest effects need to be distinguished from spurious association signals on a similar scale that may be generated as a result of artifact (e.g., informative missingness) or biological effects such as cryptic population stratification.

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