Editorial Commentary

Dissecting Hypertension by Obesity Identifies a Locus at 1p36

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The elevated arterial pressure that defines essential hypertension is regarded as the manifestation of a diverse array of interacting genetic and environmental causes. As such, hypertension is a heterogeneous disorder in which multiple contributing factors are responsible for the overarching phenotype of high blood pressure that is the primary clinical manifestation observed. Such heterogeneity has undoubtedly hampered efforts to elucidate the genetic basis of essential hypertension.

Overweight and obesity are well known to increase the risk of essential hypertension. Yet, there are many hypertensive individuals whose weight is normal. So does obesity hypertension have a different underlying genetic cause than lean hypertension? In the current issue, Pausova et al report finding a locus with suggestive linkage to hypertension and then reanalyzed their data after dividing their families into lean and obese.[1] Of considerable interest, the significance of the linkage peak increased for the obese families but disappeared in the case of the families with hypertension who were not obese. The striking contrast in results for each category of hypertension lends strong support to the idea that hypertension of obesity has a different genetic basis than other categories of hypertension. Not only is this finding important in discovery of the genetic basis of obesity hypertension, but it has obvious implications for approaches that might be used to identify the basis for other "intermediate phenotypes" of hypertension.

The study by Pausova et al involved 55 extended families from the geographically remote French-Canadian Saguenay/Lac-St-Jean region of Quebec. This relatively small, isolated population has been spared the level of genetic "noise" present in populations elsewhere. As a result, the degree of genetic homogeneity should be elevated and likely contributed to the success obtained.

The findings emanated from a whole-genome scan using microsatellite markers spread fairly uniformly across the genome. The 2 "best" loci were found on chromosomes 1 (at p36) and 11 (at p15). By changing affected status from "hypertension" to "obesity hypertension" the 1p36 locus became significant (logarithm of the odds for linkage [LOD] score=3.1), as indicated above. On the other hand, the 11p15 locus became less significant, showing that the latter was a locus for hypertension independent of obesity. Fine mapping of the 1p36 locus refined the region and increased the LOD score to 3.5. Such a score exceeds the genome-wide significance thresholds for linkage of ≥3.3 set down by Lander and Kruglyak.[2]

Pausova et al use a definition of "obesity" as a body mass index of ≥27 kg/m^2 and "nonobese" as <27 kg/m^2. This definition differs from the World Health Organization (WHO) criteria of <25 kg/m^2 for normal weight, 25 to 30 kg/m^2 for overweight, and ≥30 kg/m^2 for obese. The authors nevertheless exclude individuals with more severe obesity (>35 kg/m^2). Thus, although it might be acceptable to use the criteria described for allocating subjects to the "obese" and "nonobese" groups, the deviation from the internationally accepted definition could have implications for interpretation of data from other workers in the future who may wish to replicate the findings but by using the standard definition. Moreover, the number of "obese" families was only 15, whereas the number of "nonobese" families was 40.

The study highlights the value that can be obtained by testing robust intermediate phenotypes in the search for hypertension genes.[3] Here, despite a relatively small number of families being studied, a significant locus has emerged. This contrasts with the 2 largest genome scans for hypertension, the National Heart, Lung and Blood Institute Family Blood Pressure Program (NHLBI-FBP)[4] and the British Investigation of the Genetics of Hypertension (BRIGHT)[5] studies, which failed to find even a single locus that attained genome-wide significance (after discounting a false locus on chromosome 6 in the UK study).

In viewing all of the various genome scans for essential hypertension,[6,7] including the present one, what stands out is the remarkable inconsistency of the findings between different studies. Nevertheless, some loci do appear to show greater reproducibility than others for different cohorts. One of these is the 1p36 locus, which has shown suggestive linkage to hypertension in Australians,[8,9] Taiwanese,[10] and Sardinians,[11] and to systolic blood pressure in hypertensive Hispanic families.[12] It is thus possible that the suggestive linkage findings in these as well as other populations will turn out to be enhanced if obesity hypertension rather than general hypertension were to be examined.

Importantly, in the context of the present obesity hypertension findings, a genome scan has previously identified 1p36 as containing a quantitative trait locus for the phenotypes of obesity itself.[13] Genetic variation within a gene in the 1p36 region has also been implicated in familial combined hyperlipidemia.[14] In addition, the

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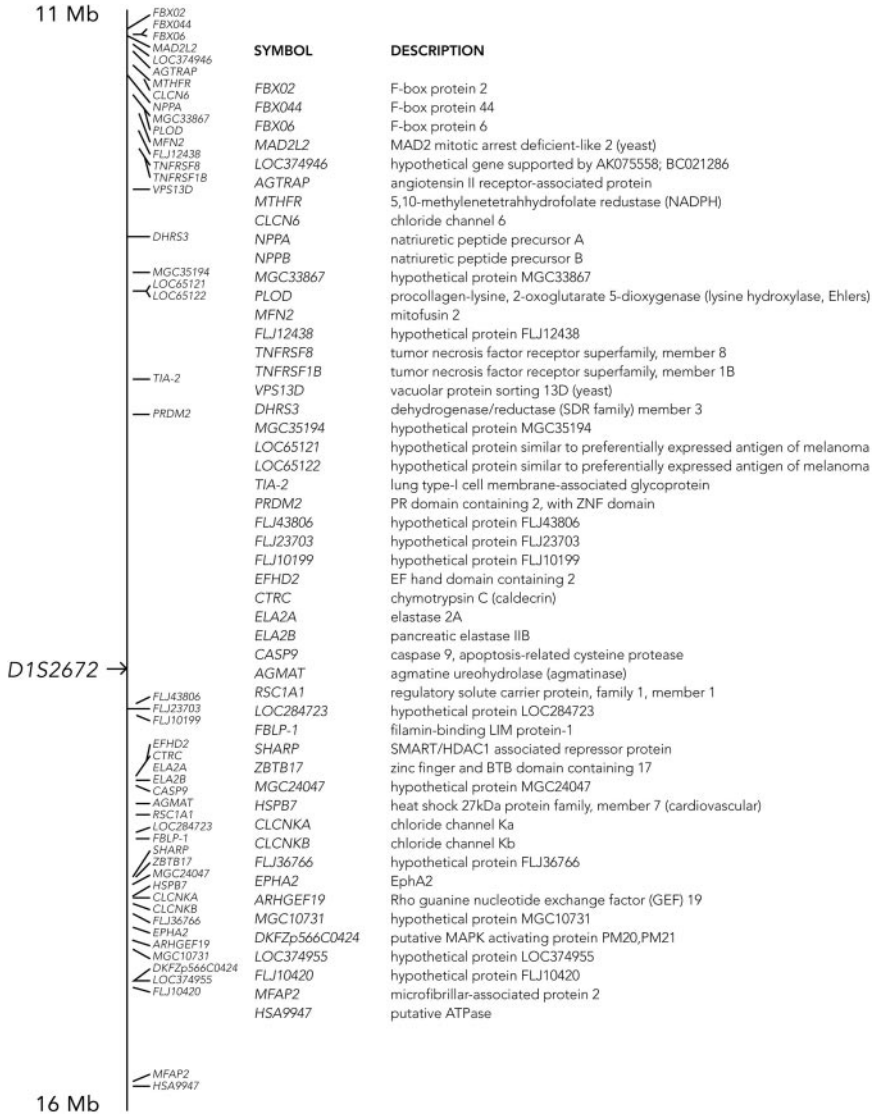

SYMBOL	DESCRIPTION
FBX02	F-box protein 2
FBX044	F-box protein 44
FBX06	F-box protein 6
MAD2L2	MAD2 mitotic arrest deficient-like 2 (yeast)
LOC374946	hypothetical gene supported by AK075558; BC021286
AGTRAP	angiotensin II receptor-associated protein
MTHFR	5,10-methylenetetrahhydrofolate redustase (NADPH)
CLCN6	chloride channel 6
NPPA	natriuretic peptide precursor A
NPPB	natriuretic peptide precursor B
MGC33867	hypothetical protein MGC33867
PLOD	procollagen-lysine, 2-oxoglutarate 5-dioxygenase (lysine hydroxylase, Ehlers)
MFN2	mitofusin 2
FLJ12438	hypothetical protein FLJ12438
TNFRSF8	tumor necrosis factor receptor superfamily, member 8
TNFRSF1B	tumor necrosis factor receptor superfamily, member 1B
VPS13D	vacuolar protein sorting 13D (yeast)
DHRS3	dehydrogenase/reductase (SDR family) member 3
MGC35194	hypothetical protein MGC35194
LOC65121	hypothetical protein similar to preferentially expressed antigen of melanoma
LOC65122	hypothetical protein similar to preferentially expressed antigen of melanoma
TIA-2	lung type-I cell membrane-associated glycoprotein
PRDM2	PR domain containing 2, with ZNF domain
FLJ43806	hypothetical protein FLJ43806
FLJ23703	hypothetical protein FLJ23703
FLJ10199	hypothetical protein FLJ10199
EFHD2	EF hand domain containing 2
CTRC	chymotrypsin C (caldecrin)
ELA2A	elastase 2A
ELA2B	pancreatic elastase IIB
CASP9	caspase 9, apoptosis-related cysteine protease
AGMAT	agmatine ureohydrolase (agmatinase)
RSC1A1	regulatory solute carrier protein, family 1, member 1
LOC284723	hypothetical protein LOC284723
FBLP-1	filamin-binding LIM protein-1
SHARP	SMART/HDAC1 associated repressor protein
ZBTB17	zinc finger and BTB domain containing 17
MGC24047	hypothetical protein MGC24047
HSPB7	heat shock 27kDa protein family, member 7 (cardiovascular)
CLCNKA	chloride channel Ka
CLCNKB	chloride channel Kb
FLJ36766	hypothetical protein FLJ36766
EPHA2	EphA2
ARHGEF19	Rho guanine nucleotide exchange factor (GEF) 19
MGC10731	hypothetical protein MGC10731
DKFZp566C0424	putative MAPK activating protein PM20,PM21
LOC374955	hypothetical protein LOC374955
FLJ10420	hypothetical protein FLJ10420
MFAP2	microfibrillar-associated protein 2
HSA9947	putative ATPase

Genes flanking the linkage peak for obesity hypertension at *D1S2672* identified within the p36 region of chromosome 1 and location (derived from information at http://www.ncbi.nlm.nih.gov/mapview/maps.cgi?TAXID=9606&CHR=1%7CCelera&MAPS=ugHs%2Cgenes%2Csts-r&QSTR=D1S2672&QUERY=uid%2849898%29&BEG=11 M&END=16 M&thmb=o). The region shown spans base pairs 11 million to 16 million from the distal end of the p arm of chromosome 1. On the right is an ordered list of 50 genes in this region, showing symbol and description of each, and on the left, are the positions of many of these (those not shown because of space limitations can be inferred from the list on the right).

chromosomal region 1p34–36 has been identified as being responsible for premature myocardial infarction.[15] It remains to be seen whether the same gene, in conjunction with other genes elsewhere in the genome (or even within the same region), will prove to be contributing to these various, somewhat overlapping, conditions.

So what could be the identity of the gene(s) responsible? Potential candidates in the 1p36 region include the chloride channel genes *CLCNKA* and *CLCNKB*, the tumor necrosis factor (TNF) receptor 2 gene *TNFRSF1B*, and the natriuretic peptide genes *NPPA* and *NPPB*. Association with hypertension has been reported for a T481S variant of *CLCNKB*[16] and an intron 4 variant of *TNFRSF1B*,[8] whereas *CLCNKA*[17] and *NPPA*[18] variants have proved negative. However, all genetic polymorphisms in the latter 2 have not been tested extensively, so before this is done, these remain as candidates. In the case of the initial *TNFRSF1B* and *CLCNKB* findings, more detailed follow-up studies in a cohort selected for enhanced biological power by having 2 affected parents, and that, not surprisingly, exhibited early onset moderate to severe hypertension, have proved negative.[19] Moreover, no association of *TNFRSF1B* variants with obesity hypertension was observed.[19] More extensive studies of these and other potential candidate genes in subjects with the phenotype of obesity hypertension are thus required to identify the gene(s) and causative variants responsible.

The Figure shows 50 genes flanking the linkage peak at *D1S2672*. As well as those mentioned above, others that stand out as being of possible interest include the angiotensin II receptor-associated protein *AGTRAP*, the methylenetetrahydrofolate reductase gene *MTHFR*, which has been implicated in myocardial infarction[20] and systemic inflammation,[21] and the mitofusin 2 gene (*MFN2*), which encodes a mitochondrial membrane protein implicated in obesity.[22] The 1p34–36 region has shown significant genome-wide linkage to premature myocardial infarction,[15] and variation in the gene *GJA4* for the gap–junction protein expressed in arterial endothelium, connexin 37, located in this region has shown strong association with myocardial infarction.[15,23]

Hypertensive subjects exhibit dyslipidemia, and genetic variation in *TNFRSF1B* is associated with plasma total, low-density and high-density lipoprotein cholesterol in hy-

pertensive subjects,[8] as well as with elevated cholesterol in familial combined hyperlipidemia.[14]

Not only does the work of Pausova et al provide an important insight into the cause of obesity hypertension, it also gives hope to those of us who have been frustrated by attempts to identify the genetic basis of hypertension by way of genome-wide linkage scans and other genetic approaches. The use of intermediate phenotypes has been long touted for facilitating an understanding of the genetic basis of essential hypertension. The new finding appears to offer the strongest support yet for this being the way of the future in the genetic dissection of the phenotype of elevated blood pressure that we call "essential hypertension." The findings are thus very encouraging in more ways than one.

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