REFERENCES

1. Lamouille S, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. *Nat Rev Mol Cell Biol* 2014; 15(3):178–96.
2. Karopadi AN, Mason G, Rettore E, Ronco C. Cost of peritoneal dialysis and haemodialysis across the world. *Nephrol Dial Transplant* 2013; 28(10):2553–69.
3. Golper TA. The possible impact of the US prospective payment system (“bundle”) on the growth of peritoneal dialysis. *Perit Dial Int* 2013; 33(6):596–9.
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High Time for Human Height

Height, a most visible characteristic in humans, is a classic quantitative trait, easy to measure with precision and directly relevant to normalize physiological functions including transport across the peritoneal membrane (1). The heritability of adult height is very high, ~80%, as demonstrated by family-based studies. For almost 100 years, it has been postulated that this genetic component reflects the combination of many genes, each accounting for a small proportion of the heritability (2). Genome-wide association studies (GWAS) performed over the last years have identified approximately 200 common variants (i.e. single nucleotide polymorphisms [SNPs], found in at least 5% of the population) associated with adult height. Although some of these variants overlap with genes involved in Mendelian disorders affecting stature (e.g., growth hormone pathway), they accounted together for only 10 – 15% of the heritability, leaving a large chunk of heritability unexplained (3). Finding the genes underlying this missing heritability is important, as it would potentially improve the understanding of human height.

By combining the results of 79 GWAS on height, amounting to 253,288 people of European ancestry, a large consortium has now identified 697 variants reaching genome-wide significance ($p < 5 \times 10^{-8}$), which together explain 16% of the genetic contribution to adult height (4). To test whether increasing the number of variants would explain more variance, they changed the significance level to $p < 5 \times 10^{-3}$ and obtained a set of ~9,500 SNPs that could explain ~29% of the height variance, i.e. the majority of heritability attributable to the ~1 million common HapMap SNPs. These results mean that larger GWAS have indeed the power to identify SNPs that explain a substantial part of the heritability in complex traits. They also confirm that the genetic architecture of height is made of thousands of common variants, each exerting a small influence on the trait.

But can these large GWAS also bring new biological knowledge? To address this crucial issue, the consortium used sophisticated analytical tools to show that the 697 genome-wide significant variants associated with height were not randomly distributed in the genome (4). In fact, these variants are enriched in putatively functional regions (e.g. non-synonymous SNPs, or *cis*-regulatory regions) and they overlap with genes underlying monogenic syndromes of abnormal height. Using *in silico* methods, they showed that the GWAS loci reveal gene associations and pathways (e.g., ossification, embryonic skeletal system development, limb development) relevant for skeletal growth and enriched for expression in tissues related to chondrocytes, endocrine and musculoskeletal tissues. Importantly, they identified pathways that were not previously known to be associated with growth, including fibroblast growth factor signaling, WNT/ β -catenin, osteoglycin and genes related to bone or cartilage development. Some of the individual genes included in these loci may also play a role in rare Mendelian disorders of human growth.

How is this remarkable study relevant for peritoneal dialysis? In fact, the study demonstrates that a high but finite number of genetic variants together account for the genetic component of human height. It can be postulated that such genetic architecture also applies to other complex traits, for instance transport across the peritoneal membrane, which itself is conditioned partly by height (1). There is a large variability of transport at the start of PD. Clinical factors account for a small part (e.g., 20%) of this variability, leaving ample space for genetic factors. Thus far, the candidate gene approach yielded useful information about the peritoneal membrane (e.g. involvement of interleukin-6 [IL-6] or endothelial nitric oxide synthase [ENOS]), although limited by study design and power (5). Large-scale investigations of the genetic determinants of peritoneal function are coming of age, owing to larger populations on peritoneal dialysis, improved techniques to assess peritoneal transport, and more uniform outcome measurements. One can predict that such association studies will yield precious information on the biological determinants of peritoneal transport and outcome in peritoneal dialysis.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

Olivier Devuyst
Deputy Editor

REFERENCES

1. Tzamaloukas AH, Murata GH, Piraino B, Malhotra D, Bernardini J, Rao P, *et al.* The relation between body size and normalized small solute clearances in continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol* 1999; 10:1575–81.
2. Weedon MN, Frayling TM. Reaching new heights: insights into the genetics of human stature. *Trends Genet* 2008; 24:595–603.
3. Durand C, Rappold GA. Height matters—from monogenic disorders to normal variation. *Nat Rev Endocrinol* 2013; 9:171–7.
4. Wood AR, Esko T, Yang J, Vedantam S, Pers TH, Gustafsson S, *et al.* Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat Genet* 2014; 46:1173–86.
5. Goffin E, Devuyst O. Phenotype and genotype: perspectives for peritoneal dialysis patients. *Nephrol Dial Transplant* 2006; 21:3018–22.

doi: 10.3747/pdi.2014.00272