editorial

A new Thematic Series: Genetics of human lipid diseases

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This millennium has witnessed a remarkable revolution in our ability to both identify and genotype DNA variation in individual human genomes with major benefits. These include enormously increasing knowledge of the etiologies of numerous diseases with a known underlying lipid component(s), identifying novel lipid-biological contributions to diseases where none were previously suspected, and generally enhancing understanding of the role of lipids in ensuring healthy physiological states. It therefore seems timely to collate these developments into a Thematic Review Series on the genetics of human lipid diseases, and to do this justice by including contributions from scientists, mathematicians, and our colleagues working with the pharmaceutical industry. This editorial considers some of the highlights that will be covered in the series of 13 reviews, focusing on the different genetic approaches that have helped accelerate the gene discovery process, with their consequent diagnostic and therapeutic implications.

One highlight is the recent discovery that sequence-alterations in *CYP7B1* (encoding cytochrome P450-7B1) segregate with an autosomal-recessive form of spastic paraplegia [OMIM #603711] (1). In brief, this story emerged from a standard genome-wide linkage scan, which returned evidence for linkage of this debilitating disorder to a region on the long arm of chromosome 8 (2). Further mapping of the region in five affected families narrowed the search for mutations to an 11Mbp stretch of DNA containing 40 annotated genes. Subsequent sequence analysis revealed disease-segregating mutations on both alleles of *CYP7B1* in all 18 affected patients, a tantalizing result, because in the brain, cytochrome P450-7B1 provides an alternative pathway for the degradation of cholesterol, as well as a means of modifying dehydroepiandrosterone neurosteroids (3). This huge and burgeoning area of central and peripheral neuropathology will be covered in two separate reviews, one by Professor Björkhem and colleagues, and the other by Professor Nave.

Another unexpected development was the discovery that P450 oxidoreductase (POR) deficiency underlies a form of congenital adrenal hyperplasia (CAH) characterized biochemically by partial defects of steroidogenic enzymes dependent on P450 for catalytic electron donation, and clinically by a combination of changes expected of disordered steroidogenesis (e.g., sexual ambiguity) along with an Antley-Bixler-like skeletal malformation [OMIM #207510]. However, embryonic lethality in mice made deficient for *POR*, and presumed equivalent major disturbance in humans whose genome is thought to encode as many as 50 functional POR-dependent Type II cytochrome P450 enzymes, delayed direct sequencing of *POR* on biological and economic grounds. In fact, it was only after the sequence of *POR* became available in the Human Genome Project Database, and overall sequencing costs dramatically fell, that the 'risk' of *POR* mutations was allowed to be investigated as a cause of this novel form of CAH, hitting paydirt (4, 5). In the forthcoming series, Professor Miller will review this and other inherited disorders of steroidogenesis and potential mechanisms by which POR deficiency may cause skeletal malformations.

Another fine example of hitting paydirt was the identification of a 3β-hydroxysterol Δ^{24}-Reductase (*DHCR24*) cDNA sequence in the GenBank sequence database, and the subsequent demonstration that mutations of this gene cause demosterolosis [OMIM #602398], a rare recessive disorder of cholesterol biosynthesis characterized by multiple lethal congenital malformations plus osteosclerosis (6). This story started classically with a thorough biochemical analysis of patient samples, which suggested that a deficiency of an enzyme designated DCHR24 might cause this devastating condition. The next giant step forward came with the identification of the causative mutations in plants displaying dwarfism and reduced fertility, and the biochemical finding that the mutated gene (*DWF1*) normally catalyzed reactions similar to those proposed for DCHR24. Professor Porter will conclude this remarkable

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story as part of his review on the inherited disorders of cholesterol biosynthesis.

In further tribute to the benefit of low cost gene sequencing, Ferdinandusse et al. (7) successfully discerned the genotype phenotype correlations of D-bifunctional protein (DBP) deficiency (OMIM #261515) by first finding the disease-causing *DBP* mutations in a cohort of 110 well-characterized patients and then assessing their predicted effects on protein structure. Thus, in the most severely affected patients, designated Type I, only deletions, insertions, and nonsense mutations were identified, whereas in Type II and III individuals, defects ranged from replacement of catalytic amino acid residues and of residues in direct contact with the enzymes' substrates and cofactors to disturbances affecting the protein fold or homodimerization of the DBP subunits. The genetics and structures involved in this and other peroxisomal fatty oxidation disorders will be critically reviewed by Professor Van Veldhoven. His review will also lay out the basic oxidation reactions carried in peroxisomes; first, to produce oxidation products crucial for human health (i.e., primary bile acids and polyunsaturated fatty acids), and second, to degrade those products (e.g., very long-chain fatty acids, phytanic acid) that would otherwise lead to the development of severe clinical disease and death within the first year of life (e.g., Type I DBP deficiency).

The ever-reducing cost of DNA sequencing has also paid dividends in population-based studies. For example, Rader and colleagues (8) were able to resequence all 10 exons of the endothelial lipase gene (*LIPG*) in 585 participants of European ancestry, 372 with extremely high HDL-C (>95th percentile) and 213 with low HDL-C (<25th percentile). They hypothesized and confirmed loss-of-function mutations, although rare, were significantly more common in the high-HDL group. Moreover, they showed that their most common (i.e., 2.2% Europeans; 2.6% African Americans) loss-of-function 'mutation' was associated with substantial increases (~8 mg/dl) in serum HDL-C, leading them to speculate that inhibition of endothelial lipase may be an effective mechanism to raise HDL-C. The results from this study and other investigations that have helped to dissect out the genetic architecture of low and high HDL-C phenotypes will be reviewed by Professor Pajukanta.

Arguably, coding exons harbor more functional variation than other gene regions, a stance that served Professors Hobbs and Cohen and colleagues well in their search for variation conferring susceptibility to nonalcoholic fatty liver disease. In short, they genotyped 9,000+ nonsynonymous sequence variants in 1,032 African Americans, 696 European Americans, and 383 Hispanics drawn from the Dallas Heart Study, identifying a highly significant association between a *PNPLA3* variant (Ile148Met) and hepatic fat content, as well as evidence of hepatic inflammation (9). Subsequent studies have confirmed this association (10) and provided protein data to endorse the exonic focus (11). It turns out that the wild-type *PNPLA3* gene product, patatin-like phospholipase domain-containing 3 protein, hydrolyses emulsified triglyceride in vitro, and that this activity is abolished by the methionine substitution. Moreover, structural modeling of this substitution offers a cogent explanation in terms of steric hindrance (11). In the forthcoming Thematic Series, Professor Burnett promises to produce a comprehensive review that brings all of us up to date with the genetics of hepatic steatosis, while Professor Hatch will provide a critique on the skeletal and cardiac muscle consequences of inherited triglyceride storage diseases, including neutral lipid storage disease with myopathy [OMIM #610717] attributable to *PNPLA2* mutations (12).

Despite some initial concerns over study costs, the genotyping of hundreds of thousands of variants scattered across the genome in a large number of people has also met with some considerable success; namely, multiple genomic regions have been identified that contain variation (albeit many in uncharacterized stretches of DNA) that quantitatively influence serum lipid levels (13–16). We are therefore extremely pleased that Professor Wijsman has agreed to include in her review an in-depth critique of the tenets of the genome-wide association (GWA) approach, its strengths and limitations, and that Professor Niemi will consider in his review the utility of GWA studies for improving drug efficacy, as well as reducing adverse drug reactions. Moreover, we look forward to the contributions from Professors Hegele and Kathiresan (Genetics of high and low serum triglyceride levels) and Professors Calandra and Tarugi (Genetics of high and low LDL-C levels). These reviews will compare and contrast the nature of the gene and gene variants modulating serum lipid levels in the population-at-large and the familial dyslipidemias. Additionally, they will cover the types of genomic and functional studies that promise to shed light on the physiological connections between the 'orphan' variants thrown up in the GWA studies and serum lipid levels.

Genetic discoveries in humans often prompt development of genetically engineered model-mice to pursue pathogenesis and evaluate both pharmaco-therapy and prevention, a strategy that has proved to be particularly attractive in the study of multi-systems disorders. One of the very many fine examples, described in the review by Professor Grabowski (Multi-system disorders of glycosphingolipid and ganglioside metabolism), is the demonstration that neural cell-specific disruption of glucosylceramide synthase leads to severe neural defects and death within 3 weeks, and that glycosphingolipid synthesis is crucial after birth for the maturation of the brain (17). Another, albeit unrelated, model that warrants further scrutiny for the understanding of lipids in human sleep disorders is that of the short-chain acyl CoA dehydrogenase deficient (*Acads*) mouse, which has significantly slower theta frequency during REM sleep than normal (18). This model ties in well with a recent GWA search for genes predisposing to narcolepsy, which identified a variant between *CPTIB* (carnitine palmitoyltransferase 1) and *CHKB* (choline kinase-β) (19). Although the mechanistic basis for this association is currently unknown, Miyagawa et al. (19) have speculated on the significance of CPT1B regulating β-oxidation, the pathway implicated in the *Acads* knock-out mice, and CHKB in the metabolism of choline, a precursor of the REM-

and wake-regulating neurotransmitter acetylcholine. And with these pointers to the role of lipids in sleep disturbance, it is time to thank all contributors (including reviewers) to the Thematic Review Series on genetics of human lipid diseases, and put this commentary to bed.

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