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GENETICS OF OBESITY AND DIABETES

34. Pharmacogenomic aspects in the treatment of type 2 diabetes

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The introduction of several new drug groups into the treatment of type 2 diabetes in the past decades leads to increased requirement of the individualized treatment approach. A personalized treatment is important from the point of view of both the efficacy and safety. The recent guidelines are based mainly on entirely phenotypic characteristics such as diabetes duration, presence of the macrovascular complications, or the risk of hypoglycemia with the use of the individual drugs. So far, the genetic knowledge is used to guide treatment in the monogenic forms of diabetes. Oral antidiabetic drugs are used for more than a half century in the treatment of type 2 diabetes. Only in the last five years intensive research has been conducted in the pharmacogenetics of these drugs based mainly on the retrospective register studies, but only a handful of associations detected in these studies were replicated. The gene variants in *CYP2C9, ABCC8/KCNJ11* and *TCF7L2* were associated with the effect of sulfonylureas. *CYP2C9* encodes sulfonylurea metabolising cytochrome P450 isoenzyme 2C9, *ABCC8* and *KCNJ11* genes encode proteins SUR1 and Kir6.2, respectively. Those proteins constitute the ATP-sensitive K^+-channel which is a therapeutic target for sulfonylureas. *TCF7L2* is a gene with the strongest association with type 2 diabetes that influences insulin secretion. *SLC47A1, ATM* and *SLC2A2* gene variants were associated with the response to metformin. *SLC47A1* and SLC2A2 encode MATE1 metformin transporter and GLUT2 glucose transporter, respectively. The function of a gene variant near *ATM* (ataxia-telangiectasia mutated) gene is probably related to activation of AMPK. In the recent years, the first studies related to the pharmacogenetics of response to DPP-4 inhibitors were published, although none of them was replicated so far. Among identified genes are *TCF7L2, CTRB1/2* encoding chymotrypsinogen, and *GLP1R* encoding the downstream therapeutic target for gliptins – GLP-1 receptor. Whilst at present there is no convincing clinical role for genotype led prescribing in type 2 diabetes, the evidence is starting to accumulate to sufficient level to justify a genotype led clinical trial that should include at least 1,000 patients. Establishment of diabetes pharmacogenetics consortia and reduction in costs of genomics might lead to some significant clinical breakthroughs in this field in a near future. With the accumulating pharmacogenetic evidence in type 2 diabetes there are reasonable expectations that genetics might help in the adjustment of drug doses to reduce severe side effects, as well as to make better therapeutic choices among the drugs available for the treatment of diabetes.

35. Genetics of obesity: consequences for personalized medicine

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Twin and family studies suggest that up to 80 % of human variance in body weight is attributable to genetic factors. Along with variants in genes predicting monogenic obesity (e.g. *LEP, MC4R, POMC*), more than 100 loci associated with common polygenic obesity have been identified to date in large-scale genome-wide association studies (GWAS). The most prominent candidate genes within these loci appear to be involved in central nervous system including neuronal regulation of feeding (e.g. *BDNF, MC4R, NEGR1*), but also insulin and adipose biology (e.g. *FTO, IRS1, MAPK3*). Despite the large number of potential candidate genes rendering rather moderate contribution to the disease, the heritability of obesity is still far from being completely understood. Nevertheless, there is increasing interest in understanding not only the molecular mechanisms explaining the observed associations between genetic variants and obesity, but also their predictive value and eventually the potential to develop novel and effective personalized treatment strategies. Therefore, studies beyond associations of genetic variants with cross-sectional measures of overall obesity will be inevitable. Not less important is testing gene x environment interactions which may help to stratify patients into most effective treatment regimes. These strategies are crucial as there is emerging evidence for the role of genetic variants in modulating the response to therapeutic options such as lifestyle intervention, pharmacotherapy and bariatric surgery. The most prominent gene associated with obesity is *FTO*, which has been shown to modify the response to lifestyle intervention (e.g. physical activity). But also defects in genes such as *MC4R* or *POMC* significantly affect the response to interventions including exercise, as well as nutritional and behavioral therapy. Moreover, bariatric surgery outcome appears to be modulated by these genes

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too. So far, the main research approaches have been focusing on established candidate genes/polymorphisms which have been shown to be associated with overall obesity. Large-scale GWAS targeting dynamic changes of body weight following therapeutic approaches including lifestyle interventions will be desirable to path new avenues in developing novel and more effective preventive and treatment strategies in obesity. Such studies have recently revealed polymorphisms in *MTIF3* whose carriers seem to benefit more from intensive lifestyle intervention than noncarriers. Moreover, a recent GWAS pointed to a new locus near *ST8SIA2* and *SLCO3A1* significantly associated with weight loss after Roux-en-Y gastric bypass (RYGB). In conclusion, whereas genetic testing of patients with syndromic forms of obesity definitely facilitates early diagnosis and personalised medicine, common genetic variants only explain a small proportion of the heritability and so, their predictive values is limited. In the future, understanding interaction of genetic variants with lifestyle will ultimately help to improve their clinical impact in regard to personalised medicine.

36. Development of adipose tissue in childhood obesity in children and relation to comorbidities

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The development of obesity begins early in life. The period between 3–6 years of age appears critical and once established, childhood obesity regularly persists into adulthood. In normal weight children the expansion of fat mass is characterized by hypertrophy and hyperplasia of adipose tissue, both being exaggerated with development of obesity. In addition to the mere expansion of fat mass, there are alterations in adipose tissue function associated with adipocyte hypertrophy, inflammation and fibrosis in adipose tissue depots, and an imbalance in adipokine secretion. As for adults, genetic associations have been identified with childhood obesity and the major predisposing genes confer an increased risk for early onset obesity as has been shown for *FTO, TMEM18* and others. While most obesity driving factors are supposed to acted centrally in the CNS by affecting food intake and energy balance, for some of them have functional effects on the adipose tissue itself. Although the consequences of obesity are generally recognized in adults, this early emergence of obesity and hence prolonged exposure not only to increased fat mass but also adipose tissue dysfunction drives the early development of obesity-related comorbidities.

37. A genome-wide association study using a custom genotyping array identifies variants in GPR158 associated with reduced energy expenditure and increased BMI and body adiposity in American Indians

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Introduction and Aim: Pima Indians living in Arizona suffer from a high prevalence of obesity, and we have previously shown that a relatively lower energy expenditure (EE) predicts weight and fat mass gain in this population, implying that energy metabolism may contribute to the pathogenesis of human obesity. Heritable factors are estimated to explain 40–70 % and 10 % of the inter-individual variance in body weight and EE, respectively. The aim of this study was to identify genetic variants that affect EE and thereby influence BMI and body fatness in Pima Indians. **Methods:** Data from 491,265 tag variants (minor allele frequency ≥ 0.05, $r^2 \geq 0.85$) derived from whole-genome sequence data of 266 Pima Indians (40 × coverage) were genotyped using an Affymetrix Axiom Custom Array in a population-based sample of 7,701 Pima Indians. Genotypes were analyzed for association with two measures of EE when subjects were non-diabetic: resting metabolic rate (RMR) after overnight fasting measured by a ventilated hood system (n = 507) and 24h EE measured in a whole-room calorimeter (n = 419). Variants associated with both measures of EE were analyzed for association with maximum lifetime BMI (n = 5 870) and percent body fat (PFAT) (n = 912). Results were adjusted for age, sex, body composition, heritage, family membership and genomic control. **Results:** Rs11014566 (A/G), located in *GPR158*, nominally associated with both measures of EE and both measures of adiposity. The G-allele associated with lower 24-h EE (β = -33 kcal/day per copy, *p* =

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1.7×10^{-3}), lower RMR (β = -31 kcal/day, $p = 9.9 \times 10^{-3}$), higher BMI (β = +1.7 %≈0.6 kg/m^2, $p = 4.7 \times 10^{-4}$) and higher PFAT (β = +0.9 %, $p = 2.9 \times 10^{-3}$). Frequency of the G allele in Pima Indians = 0.60 is much higher than in Europeans < 0.001. Rs11014566 tags 3 other variants, rs144895904, rs34673593, and rs16925884 ($r^2 = 0.86–0.99$) localized in intron 4 of *GPR158*. Experimental testing of these variants by *in vitro* dual-luciferase reporter assays showed that rs144895904 affects promoter function. *GPR158* encoding the G protein-coupled receptor 158 which is highly expressed in brain cells and interacts with two other genes *CACNA1B* (N-type voltage-gated calcium channel) and *RGS7* (regulator of G protein signaling 7), both known to affect obesity in knock-out mice. **Conclusions:** Our results suggest that common ethnic-specific variation in *GPR158* may influence EE and predispose Pima Indians to obesity. Identification of novel genes/gene pathways that influence EE and BMI in humans may lead to a better understanding of the complex pathophysiology of obesity.

38. EIF2S3 mutations are associated with X-linked MEHMO syndrome

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Aims/hypothesis: Impairment of translation initiation and its regulation within the integrated stress response (ISR) and related unfolded-protein response has been identified as a cause of several multisystemic syndromes. Here, we link MEHMO syndrome, whose genetic etiology was unknown, to this group of disorders. MEHMO is a rare X-linked syndrome characterized by obesity, profound intellectual disability, epilepsy, hypogonadism, microcephaly, and diabetes. **Methods:** Blood samples of both probands and their parents were obtained. DNA analysis by the whole exome sequencing approach was performed. The identified new variants were functionally characterized. **Results:** We have identified novel C-terminal frameshift mutation (Ile465Serfs) in the EIF2S3 gene in three families (two Slovak and one German) with MEHMO syndrome and a novel maternally inherited missense *EIF2S3* variant (c.324T > A; p.Ser108Arg) in another male patient with less severe clinical symptoms. The *EIF2S3* gene encodes the γ subunit of eukaryotic translation initiation factor 2 (eIF2), crucial for initiation of protein synthesis and regulation of the ISR. Studies in patient fibroblasts confirm increased ISR activation due to the Ile465Serfs mutation and functional assays in yeast demonstrate that the Ile465Serfs mutation impairs eIF2γ function to a greater extent than tested missense mutations, consistent with the more severe clinical phenotype of the Ile465Serfs male mutation carriers. **Conclusion:** We propose that more severe *EIF2S3* mutations cause the full MEHMO phenotype, while less deleterious mutations cause a milder form of the syndrome with only a subset of the symptoms.

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39. Unweighted gene score as a BMI predictor in Czech males

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Purpose: The role of the single nucleotide polymorphisms in obesity development is well established in populations around the world; however, simultaneous effect of more variants is not often studied. The objective of our study was to analyse the effect of gene score constructed from four common polymorphisms within the genes for FTO (rs17817449), NYD-SP18 (rs6971019), MC4R (rs17782313) and TMEM18 (rs4854344) in the population of Slavic men. **Subjects:** Adult population sample based on the post-MONICA study (1,191 males, aged). **Outcome Measures:** BMI; *FTO, MC4R, TMEM18* and *NYD-SP18* polymorphisms have been genotyped. **Methods:** Individuals have

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been examined three times within the 9 years; polymorphisms have been genotyped using PCR-RFLP. Based on the presented numbers of risky alleles, gene score was created and the associations with BMI values have been analysed. **Results:** Genotype frequencies of all analysed SNPs in Czech males are similar to the other populations. All four polymorphisms exhibit significant effect on BMI values, with the strongest effect observed in the case of *NYD-SP18* rs6971019 SNP ($P < 0.001$) and the weakest effect was found for *TMEM18* rs4854344 polymorphism ($P = 0.05$). For 1,142 subjects, all four SNPs of interest have been successfully genotyped and the obtained range of unweighted gene score values was between 1 and 8 points. There was a strongly significant ($P < 0.00005$) linear trend of BMI values from subjects with score values 1 + 2 ($N = 36$; BMI = 27.2 ± 5.2 kg/m^2) until subjects with the highest gene score 7 + 8 ($N = 202$; BMI = 29.1 ± 4.1 kg/m^2). Similar results have been detected in examinations 2 and 3. **Conclusions:** Results suggest that unweighted gene score constructed from four polymorphisms within the genes for FTO, NYD-SP18, TMEM18 and MC4R is a strong predictor of BMI values in males.

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