Searchable abstracts of presentations at key conferences in endocrinology ISSN 1470-3947 (print) | ISSN 1479-6848 (online)

Endocrine Abstracts

published by bioscientifica

Endocrine Abstracts (2020) **70** AEP246 | DOI: 10.1530/endoabs.70.AEP246

Diabetes, Obesity, Metabolism and Nutrition

Insights from whole exome sequencing in a Maltese cohort with gestational diabetes

Nikolai Paul Pace[1,2], Barbara Vella[1], Johann Craus[1], Samir Abou-Hussein[1], Ruth Caruana[1], Alex Felice[2], Charles Savona-Ventura[1] & Josanne Vassallo[1,2]

Author affiliations

Background: Gestational diabetes (GDM) can be driven by mutations or rare variants in various genes associated with monogenic or atypical forms of diabetes. The reported frequency of monogenic defects of beta cell function in GDM varies extensively, in part due to differences in ethnicity, patient ascertainment criteria and techniques used for genetic analysis. The objective was to evaluate the frequency and molecular spectrum of mutations in a curated list of genes associated with monogenic/atypical diabetes in non-obese women of Maltese ethnicity with GDM.

Method: 30 non-obese Maltese women who met the International Association of the Diabetes and Pregnancy Study Group (IADPSG) criteria for diagnosis of GDM and with a first-degree relative with non-autoimmune diabetes were included in this study. Whole exome capture and high throughput sequencing was carried out. Rare sequence variants were filtered, annotated and prioritized according to the American College for Medical Genetics guidelines. For selected missense variants we explored effects on protein stability and structure through homology predictions or PDB structures using in-silico tools.

Results: In total, we identified three pathogenic mutations and twelve variants of uncertain significance (VUS). The disease-causing mutations comprise a nonsense mutation in *GCK*, an insertion-frameshift at a mutational hotspot in *HNF1A* and a missense substitution in *ABCC8*. Critically, the *ABCC8* mutation leads to significant changes in interatomic interactions and to expansion of protein cavity volume, with resulting destabilising effects. Damaging VUS in *PDX1, KLF11, DYRK1B, TRMT10A, AKT2, BLK, GLIS3* and *NKX6-1* were detected, having either conflicting pathogenicity interpretationsor insufficient evidence for pathogenicity from in-vitro studies. Novel *NEUROG3* and *CEL* VUS were also detected. Stereochemical analysis reveals that the missense variants described in *NEUROG3, DYRK1B, TRMT10A*and*AKT2* have destabilising effects. Genotype-phenotype correlations for all detected variants are described, including associations with anthropometric traits, OGTT, HOMA-IR, treatment and post-pregnancy follow-up data where available. We show that GDM cases

who were carriers of either pathogenic mutations or damaging VUS had a younger age of GDM diagnosis than females where no variant of interest was identified. (29 vs 32 years, $P = 0.039$).

Conclusion: This study provides the first insightinto an underlying monogenic aetiology in non-obese women with GDM from a high-prevalence island population. It suggests that monogenic variants constitute an underestimated cause of diabetes detected in pregnancy, and that careful evaluation of GDM probands to identify monogenic disease subtypes is indicated.

Felice Alex

Savona-Ventura Charles

Vassallo Josanne

Endocrine Abstracts
ISSN 1470-3947 (print) | ISSN 1479-6848 (online)