Results: The detection rates were CT 17/19 [89.5%, 95% CI = 66.9%-98.7%], MRI 17/17 [100%, 95% CI = 80.5%-100%], 18F-FDG PET/CT 16/17 [94.1%, 95% CI = 80.5%-100%], 68Ga-DOTATATE 5/9 [55.6%, 95% CI = 21.2%-86.3%], 18F-DOPA 12/14 [85.7%, 95% CI = 57.2%-98.2%], and 18F-DA 4/6 [66.7%, 95% CI = 22.3%-95.7%]. All McNemar tests showed p-values greater than 0.05, which were not statistically significant.

Conclusion: The study was performed in a small patient set with VHL-related PHEO showed MRI, with the highest detection percent followed by 18F-FDG PET/CT. More trials with a larger patient set are needed to support the statistical relevance as it was not seen in this study. Furthermore, performing a study on a patient cohort with additional VHL associated cancers could prove clinically beneficial for patients.

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Adrenal
RF33 | PSAT69
A Combined Candidate Gene/Whole Exome Sequencing Approach Permits a Rapid Genetic Diagnosis for >81% Individuals with Primary Adrenal Insufficiency.

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Introduction: Mutations in MC2R causing familial glucocorticoid deficiency (FGD), a rare form of primary, isolated adrenal insufficiency, were first published in 1993, discovered by candidate gene sequencing (CGS). Through advances in genetic techniques from homozygosity mapping to whole exome sequencing (WES) we have linked a further five genes to adrenal insufficiency and, in conjunction with other groups, this has expanded the number of mono-genic causes for isolated or syndromic adrenal insufficiency to >25.

Patients and Methods: Over the last 30 years over 400 individuals with suspected FGD, from 31 different countries, have been referred to our centre for genetic testing, ranging in age from neonates to individuals in their eighties. All cases had low or undetectable serum cortisol usually paired with an elevated plasma ACTH level. Our strategy for sequencing has evolved over time and we now routinely sequence the small, frequently mutated, candidate genes by Sanger sequencing (MC2R, MRAP, STAR and CYP11A1) before proceeding to WES as the most cost-effective route to a genetic diagnosis. In total, 369 of the 400 individuals have been fully characterised either by CGS or WES. For CGS, sequences were analysed by alignment to reference sequences using BioEdit software and for WES variant call files were initially analysed using
Ingenuity Variant Analysis package and/or examination of BAM files, using the Integrative Genomics Viewer, to detect exonic deletions. Rare, synonymous or predicted benign variants were further tested by an in vitro splicing assay using the pET01 vector (MoBiTec)

**Results:** In 308/ 369 individuals we found a definitive diagnosis in a gene known to be causal for adrenal insufficiency, giving a success rate of >81%, and identified 15 novel mutations. The aetiologies of diagnosed cases were as follows; MC2R (22%), MRAP (17%), NNT (15%), STAR (9%), CYP11A1 (7%), with the remaining 30% due to a further 13 genes.

Founder effects were clear for variants in some genes/populations, whereas in others hotspot mutations were present in multiple ethnicities. Examples include the previously described S74I in MC2R and rs6161 in CYP11A1 in the UK population, P24Rfs*4 in MCM4 in Ireland, R188C in STAR in Canada, and newly discovered associations with T731= in NNT in Sudan and R222Q in SGPL1 in Saudi Arabia. Whereas MRAP splice mutations commonly seen at the exon 3/intron 3 junction were present in individuals from many countries. The work has also highlighted a number of causal synonymous and predicted benign variants that result in splicing defects.

**Conclusion:** The use of CGS/WES now permits a rapid genetic diagnosis for >83% individuals with PAI improving tailored patient management. For the remaining patients it is unclear whether they have unconventional mutations in known genes or if there are further gene defects to be discovered.

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