Genetics of Familial Glucocorticoid Deficiency over the Decades: Phenotypic Variability and Associated Features

Smith C, Maharaj AV, Qamar Y, Prasad R, Hughes CR, Clark AJL, Chan LF, Metherell LA

Centre for Endocrinology, William Harvey Research Institute, QMUL

Introduction

Over the last 25 years more than 435 case with suspected Familial Glucocorticoid Deficiency (FGD) have been referred to our centre for genetic testing. All cases had low or undetectable serum cortisol paired with an elevated plasma ACTH level. Our patient cohort comprises over 430 patients from 30 different nationalities and ranges from neonates to patients in their eighties. 64% of patients were referred from Europe (Fig. 1a,b).

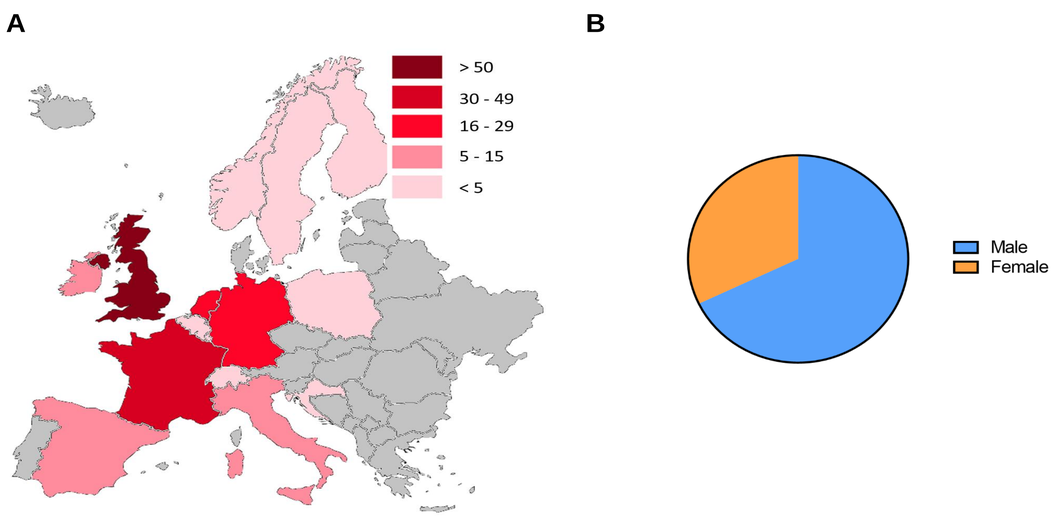

Figure 1: The demographic of our cohort. A. A map detailing the country of birth and patient numbers referred from Europe in our cohort. UK – 121, Turkey – 45 (not shown), France – 39, Germany – 17, Netherlands – 16, Italy – 11, Spain – 10, Ireland – 9, Switzerland – 2, Finland – 2, Poland – 2, Croatia – 1, Belgium – 1, Sweden – 1, Norway – 1, Luxemburg – 1. **B**. The sex of patients in our European cohort, 67% male, 33% female.

Results

Mutations in *MC2R* were first discovered in 1993, by candidate gene sequencing. 14 causal FGD genes have been identified in our cohort with varying frequencies (Figs. 2,3). Within Europe *MC2R* and MRAP are the most prevalent and there is evidence of founder effects, in particular the S74I mutation in *MC2R* in UK/Irish populations (Figs. 4,5). The causative genes are involved in diverse pathways and the resulting phenotypes are caused by defective ACTH signalling, cholesterol transport, steroidogenesis, cellular redox homeostasis, DNA replication or sphingolipid metabolism. In addition, a few cases have revealed syndromic disease exemplified by the ethnically isolated population with a *MCM4* variant causing natural killer (NK) cell and glucocorticoid deficiency with DNA repair defect and *SGPL1* mutations which cause a syndrome of primary adrenal insufficiency, progressive renal dysfunction plus in some cases ichthyosis, acanthosis, immunodeficiency and neurologic defects.

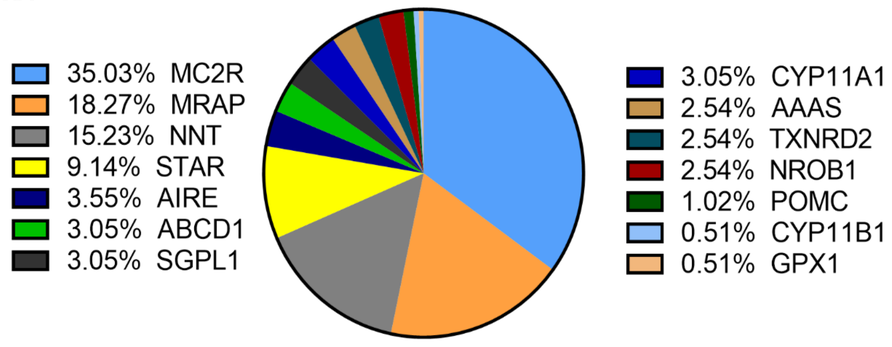

Figure 2: Mutated genes identified in cohort. MC2R mutations (Type I) constitute 35% of cases, MRAP (Type II) constitute 18% and novel mutations (Type III) constitute the rest of the cases.

Objective and methods

To determine the underlying cause of FGD by Sanger, targeted or whole exome sequencing techniques.

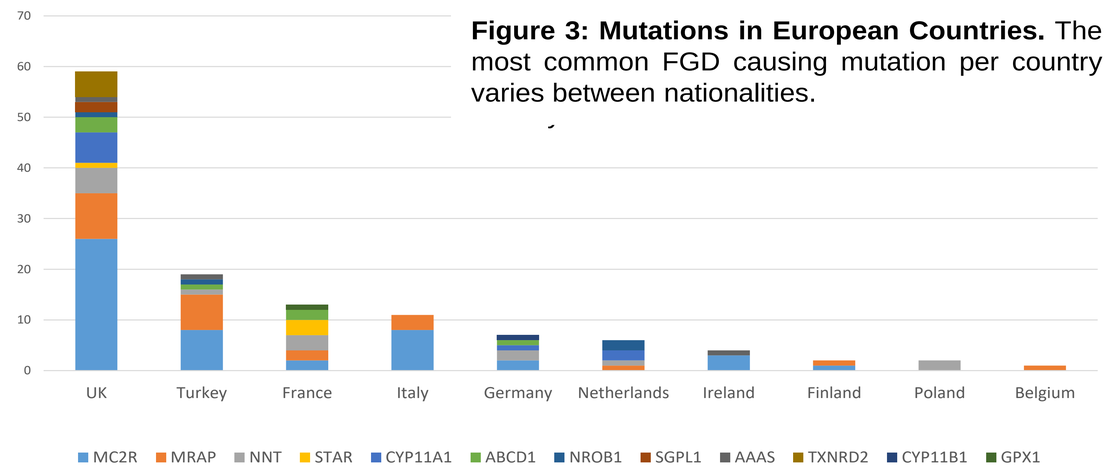

Figure 3: Mutations in European Countries. The most common FGD causing mutation per country varies between nationalities.

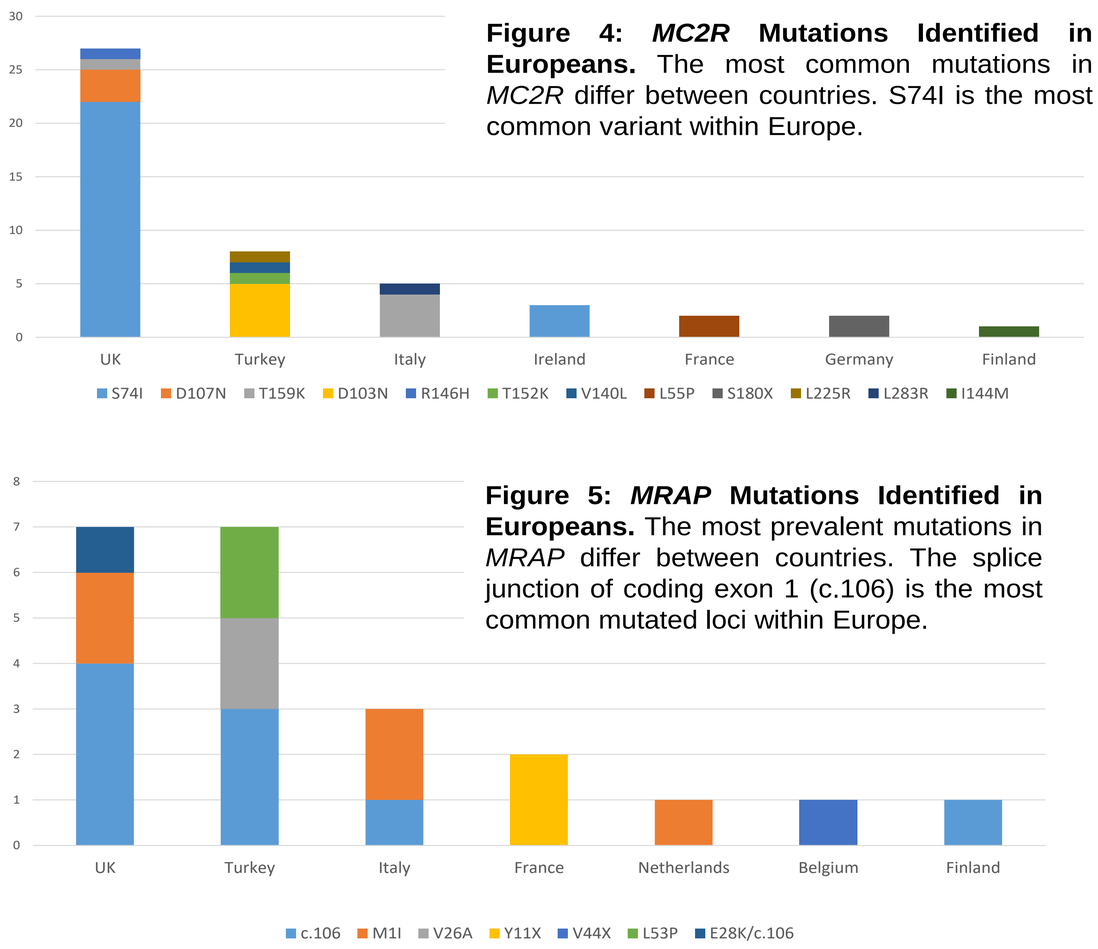

Figure 4: *MC2R* Mutations Identified in Europeans. The most common mutations in *MC2R* differ between countries. S74I is the most common variant within Europe.

Figure 5: *MRAP* Mutations Identified in Europeans. The most prevalent mutations in *MRAP* differ between countries. The splice junction of coding exon 1 (c.106) is the most common mutated loci within Europe.

Conclusions

- The work has highlighted 'mild' presentations of several adrenal insufficiency disorders, in particular non-classical presentations of lipoid congenital adrenal hyperplasia and P450 side chain cleavage enzyme deficiency with partial loss-of-function variants in *STAR* and *CYP11A1* respectively
- Future studies, to decipher whether causative defects are in non-coding parts of known genes, are due to copy number variation or novel genetic aetiologies will form improve genetic diagnosis of patients presenting with FGD.

c.j.smith@qmul.ac.uk

58ESPE RFC13-005
Adrenals and HPA Axis
CJ Smith
Poster presented at: ESPE 2019 VIENNA
PosterSessionOnline.com