Genetic analysis of pediatric primary adrenal insufficiency of unknown etiology: 25 years' experience in the UK

F. BUONOCORE[1], A. MAHARAJ[2], Y. QAMAR[2], K. KOEHLER[3], J. P. SUNTHARALINGHAM[1], L. F. CHAN[2], B. FERRAZ-DE-SOUZA[1], C. R. HUGHES[2], L. LIN[1], R. PRASAD[2], J. ALLGROVE[4], E. T. ANDREWS[5], C. R. BUCHANAN[6], T. D. CHEETHAM[7], E. C. CROWNE[8], J. H. DAVIES[5,9], J. W. GREGORY[10], P. C. HINDMARSH[11], T. HULSE[12], N. P. KRONE[13], P. SHAH[2,4], M. G. SHAIKH[14], C. ROBERTS[15], P. E. CLAYTON[16], M. T. DATTANI[1], N. S. THOMAS[17], A. HUEBNER[3], A. J. CLARK[2], L. A. METHERELL[2]*, AND J. C. ACHERMANN[1]*

[1]UCL GOS Institute of Child Health, London, UK; [2]Queen Mary University of London, London, UK; [3]Technische Universität Dresden, Dresden, Germany; [4]Barts Health NHS Trust, London, UK; [5]University Hospital Southampton NHS Foundation Trust, Southampton, UK; [6]King's College Hospital NHS Foundation Trust, London, UK; [7]Newcastle University and Great North Children's Hospital, Newcastle upon Tyne, UK; [8] University Hospitals Bristol, Bristol, UK; [9] University of Southampton, Southampton, UK; [10] Cardiff University, Cardiff, UK; [11]University College London Hospitals, London, UK; [12]Guy's and St Thomas' NHS Trust, London, UK; [13]Sheffield Children's Hospital, Sheffield, UK; [14]Royal Hospital for Children, NHS Greater Glasgow and Clyde, Glasgow, UK; [15]International Centre for Life, Newcastle, UK; [16]Manchester University Hospital NHS Foundation Trust, Manchester, UK; [17]Salisbury District Hospital, Salisbury, UK. *Last two authors contributed equally.

Introduction

- Primary adrenal insufficiency (PAI) is a potentially life-threatening condition that requires appropriate diagnosis and treatment
- The most common cause of PAI is congenital adrenal hyperplasia (CAH), but other well-established aetiologies include metabolic and autoimmune disorders, and physical damage
- In addition, pathogenic variants in more than 30 genes have now been associated with PAI, with considerable biochemical and phenotypic overlap. It is therefore important to adopt comprehensive genetic analysis to help reach a diagnosis

Aim

➢ We report the molecular basis underlying PAI in children and young people over a 25 year-period, combining published and unpublished data from our research centres

Methods

Patient cohort

- 155 children with PAI of unknown aetiology from the UK studied at three research centres from 1993 until 2018
- Children with CAH, metabolic and autoimmune causes of PAI were excluded
- An additional sub-group of 51 patients were included where a genetic diagnosis of X-linked adrenal hypoplasia congenita (AHC) due to pathogenic variants in *NR0B1* (DAX-1) had been established through clinical genetic testing services

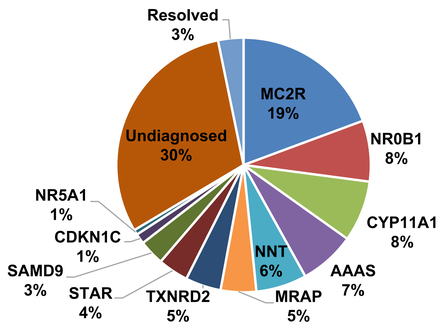
Genetic analysis

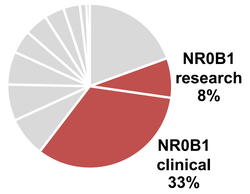
- Sanger sequencing and a candidate gene approach (1993 onwards) or next generation sequencing (NGS), using both targeted panels and whole exome sequencing (WES) (2013-2018)

Results

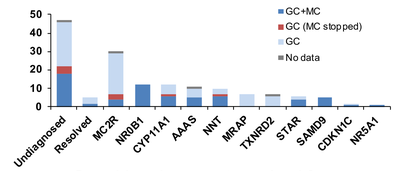
- A genetic diagnosis was identified in 103/155 (66.5%) individuals in the research cohort
- Pathogenic variants were found in eleven different genes
- PAI resolved in 3% of children and no genetic cause was found in this group

Results

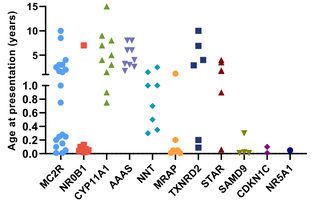




X-linked AHC was the largest diagnostic group overall

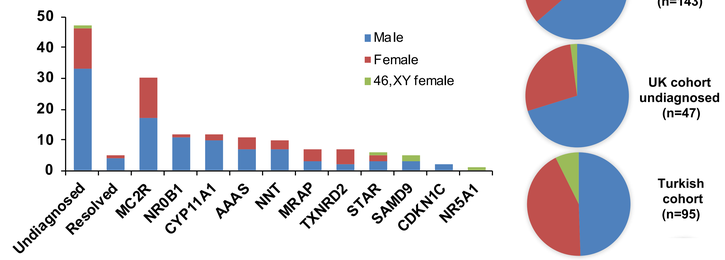


Steroid replacement received for each diagnostic group
(GC, glucocorticoids; MC, mineralocorticoids)



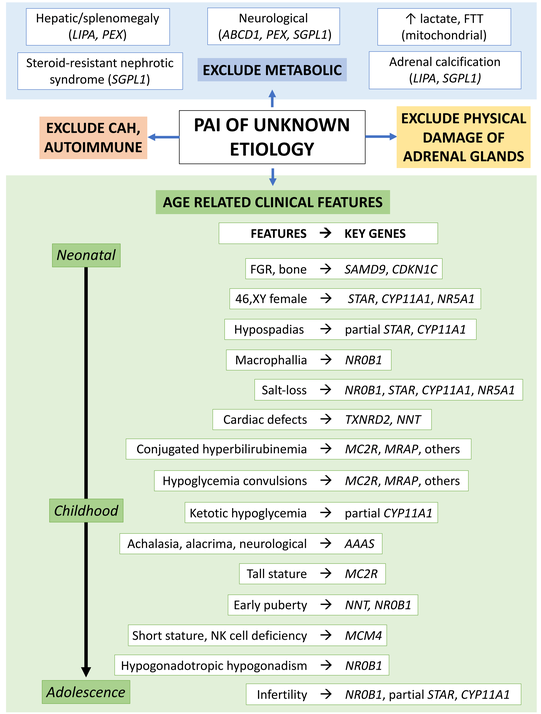
Age of main presentation of PAI for each diagnostic group

- An excess of boys was observed, even when individuals with X-linked AHC were excluded from analysis
- This difference in sex ratio was even more marked in the "undiagnosed" group of patients



Conclusions

- Although age at presentation, treatment, and other factors such as ancestral background and birthweight can provide diagnostic clues, genetic testing was required to establish the definitive cause
- NGS approaches improve the diagnostic yield when many potential candidate genes are involved
- Defining the specific aetiology has important implications for affected individuals and their families for the management of this lifelong condition:
  - ➢ monitoring associated features
  - ➢ counselling about recurrence risk in families
  - ➢ predicting disease course and modifying treatment



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