Tumour risks and genotype–phenotype–proteotype analysis of patients with germline mutations in the succinate dehydrogenase subunit genes *SDHB*, *SDHC*, and *SDHD*

Katrina A Andrews, Lindsey Vialard, David B Ascher, Douglas E V Pires, Nicola Bradshaw, Trevor Cole, Jackie Cook, Richard Irving, Ajith Kumar, Fiona Lalloo, Louise Izatt, David Goudie, Emma R Woodward, Eamonn R Maher, and the UK SDH Collaborative Group

Abstract

Background **Germline mutations in the succinate dehydrogenase subunit genes *SDHB*, *SDHC*, and *SDHD* are the most frequent causes of inherited phaeochromocytomas and paragangliomas. Insufficient information regarding penetrance and phenotypic variability hinders optimum management of mutation carriers. Our aim was to provide estimates of penetrance and genotype–phenotype correlations in a large cohort of succinate dehydrogenase mutation carriers.**

Methods **We undertook a retrospective survey of 800 individuals in the UK (401 previously reported) with germline mutations in *SDHB* (620), *SDHC* (31), and *SDHD* (149). We estimated and compared tumour risks for each gene according to age using survival analysis and Cox proportional hazards modelling with the statistical programming language R. DUET, a computational approach for predicting the effects of mutations on protein stability, was used to evaluate the functional effects of *SDHB* and *SDHD* mutations.**

Findings **Analysis of age-related tumour risks provided novel estimates of penetrance. In addition to tumour-specific differences in risk for individual genes, we confirmed that the *SDHD* p.Pro81Leu mutation had a distinct phenotype, with a low risk of phaeochromocytoma and extra-adrenal paraganglioma (only one case in 55 patients), and found evidence suggesting higher penetrance with *SDHB* p.Ile127Ser mutations. Comparison of age-dependent penetrance of disease in p.Ile127Ser carriers versus other *SDHB* missense mutation carriers showed that p.Ile127Ser was associated with a higher overall penetrance of phaeochromocytoma and paraganglioma (χ^2=4·49, p=0·034). *SDHB* p.Ile127Ser was predicted by DUET to be the most destabilising *SDHB* missense mutation, through disruption of key intramolecular hydrophobic interactions by the introduction of a polar serine. The penetrance in *SDHB* and *SDHD* mutation-positive non-probands by age 60 years was 22·1% (95% CI 15·6–28·3) and 47·5% (29·3–61·1), respectively, and the risk of malignant disease at age 60 years in non-proband *SDHB* mutation carriers was 4·2% (1·1–7·2).**

Interpretation **Increased knowledge of the lifetime tumour risks is crucial to long-term surveillance and management. Knowledge of the molecular basis of the phenotypic variability commonly observed in individuals with germline *SDHB*, *SDHC*, and *SDHD* mutations will facilitate the development of personalised management based on gene-specific and mutation-specific tumour risks.**

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University of Cambridge, Cambridge, UK (K A Andrews MBBChir, D B Ascher PhD, D E V Pires PhD, Prof E R Maher FMedSci)**; NIHR Cambridge Biomedical Research Centre, Cambridge, UK** (K A Andrews, E R Maher)**; Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK** (K A Andrews, E R Maher)**; Birmingham Women's Hospital, Birmingham, UK** (L Vialard PhD, T Cole MBChB, E R Woodward MD)**; Southern General Hospital, Glasgow, UK** (N Bradshaw MSc)**; Sheffield Children's Hospital, Sheffield, UK** (J Cook MD)**; Queen Elizabeth Hospital Birmingham, Birmingham, UK** (R Irving MD)**; Great Ormond Street Hospital, London, UK** (A Kumar MD)**; Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK** (F Lalloo MD)**; Guy's and St Thomas' Hospital, London, UK** (L Izatt MBBChir)**; and Ninewells Hospital and Medical School, Dundee, UK** (D Goudie MD)

Correspondence to:
Dr Katrina A Andrews, Academic Department of Medical Genetics, Level 6, Addenbrooke's Treatment Centre, Cambridge CB2 0QQ, UK
kandrews1@doctors.org.uk

Contributors

ERM set up the project, applied for ethics approval, and designed and distributed the clinical information request forms. LV, NB, TC, JC, RI, AK, FL, LI, DG, and ERW were prominent members of the UK SDH collaborative group. DBA and DEVP created the SDHB and SDHD in-silico structural model and provided DUET scores. KAA collected and analysed the data and wrote the abstract under supervision of ERM.

Declaration of interests

We declare no competing interests.

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