THEMATIC RESEARCH

Distortion in transmission of pathogenic *SDHB*- and *SDHD*-mutated alleles from parent to offspring

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Abstract

Phaeochromocytoma and paraganglioma are highly heritable tumours; half of those associated with a germline mutation are caused by mutations in genes for Krebs's cycle enzymes, including *succinate dehydrogenase* (*SDH*). Inheritance of *SDH* alleles is assumed to be Mendelian (probability of 50% from each parent). The departure from transmission of parental alleles in a ratio of 1:1 is termed transmission ratio distortion (TRD). We sought to assess whether TRD occurs in the transmission of *SDHB* pathogenic variants (PVs). This study was conducted with 41 families of a discovery cohort from Royal North Shore Hospital, Australia, and 41 families from a validation cohort from St. Bartholomew's Hospital, United Kingdom (UK). Inclusion criteria were a clinically diagnosed *SDHB* PV and a pedigree available for at least two generations. TRD was assessed in 575 participants with the exact binomial test. The transmission ratio for *SDHB* PV was 0.59 ($P = 0.005$) in the discovery cohort, 0.67 ($P < 0.001$) in the validation cohort, and 0.63 ($P < 0.001$) in the combined cohort. No parent-of-origin effect was observed. TRD remained significant after adjusting for potential confounders: 0.67 ($P < 0.001$) excluding families with incomplete family size data; 0.58 ($P < 0.001$) when probands were excluded. TRD was also evident for *SDHD* PVs in a cohort of 81 patients from 13 families from the UK. The reason for TRD of *SDHB* and *SDHD* PVs is unknown, but we hypothesize a survival advantage selected during early embryogenesis. The existence of TRD for *SDHB* and *SDHD* has implications for reproductive counselling, and further research into the heterozygote state.

Key Words

- phaeochromocytoma
- molecular genetics

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Introduction

The phaeochromocytoma and paraganglioma (PPGL) tumour group is the most heritable of tumours, with at least 40% of cases arising from a pathogenic germline mutation (Dahia 2014). Of these, around half are caused by pathogenic variants (PVs) in genes encoding critical enzymes of the tricarboxylic acid cycle, including *succinate dehydrogenase (SDH).* PVs in *SDH* subunits result in loss of function of the SDH protein complex; *SDH*-deficient tumours are in the cluster of PPGL with a pseudo-hypoxic cellular response and the greatest potential for metastatic disease (Nölting *et al.* 2022), and the metastatic tendency is particularly apparent with PVs in the *SDHB* subunit. Inheritance of *SDH* alleles is assumed to follow Mendelian laws of segregation, with a probability of 50% from each parent, but confirmation of this in clinical practice is made difficult by the highly variable penetrance across the subunits *SDH-A* to *-D* (Tufton *et al.* 2019) and the rarity of *SDH*-deficient tumours in general.

There exist monogenic familial diseases which are not necessarily transmitted according to Mendelian laws of inheritance, including Factor V Leiden deficiency (Infante-Rivard & Weinberg 2005), Long QT syndrome (Imboden *et al.* 2006), and some of the spinocerebellar ataxias (Riess *et al.* 1997, Bettencourt *et al.* 2008) (Table 1). The departure from a transmission of parental alleles in a ratio of 1:1 is termed transmission ratio distortion (TRD) (Pardo-Manuel de Villena *et al.* 2000). There are five key timepoints at which TRD can occur (Huang *et al.* 2013): (i) germline selection (e.g. mutation, recombination, non-allelic gene conversion) during mitosis; (ii) mechanisms that occur in meiosis and prior to fertilization known as meiotic drive, where the structural characteristics of a certain chromatid result in increased transmission during oogenesis (maternal germline) or spermatogenesis (paternal germline); (iii) gametic competition (by sperm) prior to fertilization, resulting in gamete selection; (iv) imprint resetting at the post-implantation stage, when parental imprints are erased and re-established; and (v)

Table 1 Genes known to demonstrate transmission ratio distortion.

Gene	Function
	Relates to tumourigenesis
CDKN1C	Tumour suppressor
HRAS1	Oncogene
IGF2	Intestinal adenoma
RB-1	Retinoblastoma tumour suppressor
SIRT3	Node-positive breast cancer
TNFa and *TNFb*	Tumour necrosis
	Relates to neurological development
ARX	Non-syndromic intellectual disability and brain malformations
CTDP1	Congenital cataract, facial dysmorphism, peripheral neuropathy
DMPK	Muscular dystrophy
HASH2 (ASCL2)	Neuronal precursor for central and peripheral nervous systems
SCA1, SCA3 (ATXN3)	Spinocerebellar ataxia types 1 and 3 (respectively)
SMN1	Spinal muscular atrophy
TH	Neuropathology
	Overlap of roles in tumourigenesis and early neurological development
DBC1, CDK5RAP2, MEGF9	Neuronal differentiation; bladder cancer
MTHFR	Acute leukaemia; colon cancer; neural tube defects
NBPF8 and *HFE2*	Neuroblastoma tumour suppressor, cognitive development; iron metabolism
	Other
ATG16L1, DLG5	Inflammatory bowel disease
BHLHA9	Split-hand/foot malformation +/– Long bone deficiency
CLC1, IGFR2 (FCGR2B)	Autoimmunity
F2 (Factor II / thrombin)	Thrombosis
F5 (Factor V Leiden)	Thrombophilia
HSP70.1	Graft vs host disease
INS	Hyperinsulinism
KCNQ1, KCNH2	Long QT syndrome
STX16-GNAS	Autosomal dominant pseudohypoparathyroidism type 1b
SUPT3H-MIRN586-RUNX2	Cleft palate; skeletal morphogenesis; haematological neoplasia
TGFB1	Cystic fibrosis severity and endophenotype

Data from Huang *et al.* (2013). See references for further details.

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post-fertilization mechanisms of embryonic or neonatal lethality from the inherited allele, resulting in differential survival of offspring. We suggest that at this time point, advantageous selection may also occur (Fig. 1).

Our interest in whether *SDH* PVs are inherited according to Mendelian laws of segregation or in an imbalanced, distorted way arose anecdotally: an *SDHB* PV carrier underwent pre-implantation genetic testing and reported that high numbers of embryos harboured the affected allele. We sought to assess whether TRD occurs in the transmission of *SDHB* PVs and posit that a post-fertilization survival advantage is the cause.

Materials and methods

This study has been conducted with 41 families of a discovery cohort in Australia, from Royal North Shore Hospital (RNSH), and a validation cohort in the United Kingdom, from St. Bartholomew's Hospital (SBH), together representing a range of different PVs in the *SDHB* gene. Inclusion criteria were a confirmed *SDHB* PV and a pedigree available for at least two generations (such that data on transmission could be analysed from the second generation onwards). Probands were defined as the first individual in a family to be diagnosed with an *SDHB* PV after presenting with a PPGL. PVs were classified as loss of function (nonsense, splicing, deletion, or frameshift) or missense. PVs were defined as being in the proximal region of the *SDHB* gene if they occurred in exons 1–3 or intronic regions up to IVS3. Ethics approval was obtained from the Northern Sydney Local Health District Ethics Committee for the discovery cohort (Ref: 2022/ETH01880), including waiver of consent, and Cambridge East Medical Research Ethics Committee for the validation cohort (Ref: 06/Q0104/133). Patients provided consent after a full explanation of the purpose of the study.

Statistical analysis was performed using IBM SPSS version 28. The forest plot figure was produced using GraphPad Prism version 9. Categorical data were tested with the binomial test to obtain a true estimate, with 95% confidence intervals using the Clopper–Pearson method. Continuous data were assessed with the exact Mann–Whitney test for non-parametric data. A P-value ≤ 0.05 (two-tailed) was considered statistically significant. Results that were not significant were assessed for heterogeneity with Levene's test. Several sensitivity analyses were undertaken in this study by (i) excluding probands, (ii) excluding families with incomplete family pedigree data, and (iii) excluding untested participants younger than 20 years of age. Potential predictors of TRD were assessed in the cohort that underwent genetic testing and the cohort with complete family data, using a generalized linear model with binary logistic regression to perform a multivariate analysis. Explanatory variables included in this model were sex, genotype, parent of origin, birth order, and family size.

Results

A total of 575 participants from 82 families from RNSH and SBH were assessed. There was a difference between centres in the proportion that underwent genetic testing and the number of generations assessed in each family (Table 2). Of the 575 participants assessed, 503 underwent genetic testing, with 316 found to harbour an *SDHB* PV. Thirty-six different *SDHB* PVs were represented in the combined cohort: 12 missense PVs were present in 29 families, and a further 24 PVs were loss of function mutations (Supplementary Table 1, see section on supplementary

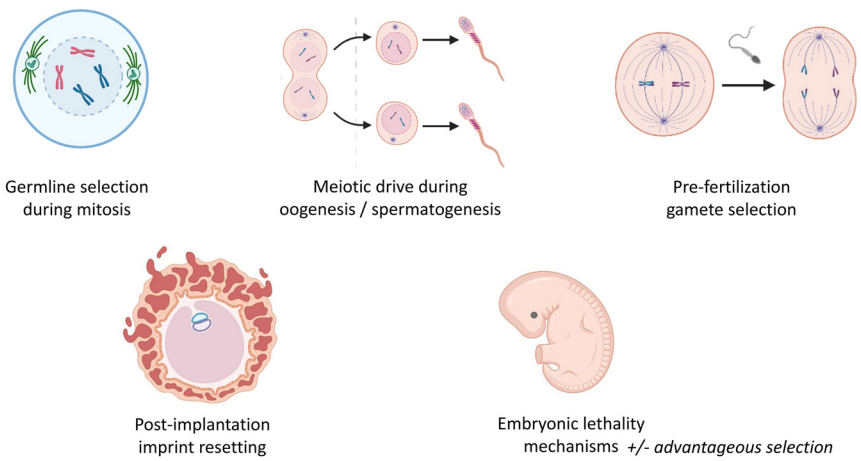

Figure 1
Five key timepoints at which transmission ratio distortion may occur. Created with https://www.biorender.com/.

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Table 2 Baseline characteristics of *SDHB* cohorts.

	RNSH – discovery cohort ($n = 279$)	**SBH – validation cohort** ($n = 296$)	**RNSH and SBH – combined cohort** ($n = 575$)	***P*-value**
Male, *n* (%)	133 (48)	149 (50)	282 (49)	0.48
Probands, *n* (%)	32 (11)	25 (8)	57 (10)	0.23
Genetic testing, *n* (%)	260 (93)	243 (82)	503 (88)	<0.001[b]
Loss of function pathogenic variant, *n* (%)	172 (62)	179 (60)	351 (61)	0.77
Birth order				
First, *n* (%)	49 (18)	120 (41)	169 (29)	0.43
Second, *n* (%)	47 (17)	96 (32)	143 (25)	
Third or later, *n* (%)	39 (14)	64 (22)	103 (18)	
Not available, *n* (%)	144 (52)	16 (5)	160 (28)	
Family size: children				
One, *n* (%)	15 (5)	20 (7)	35 (6)	0.08
Two, *n* (%)	71 (25)	120 (41)	190 (33)	
Three or more, *n* (%)	188 (67)	156 (53)	345 (60)	
Not available, *n* (%)	5 (2)	0	5 (1)	
Family size: generations				
Two; *n* families (%)	18 (44)	11 (27)	29 (35)	0.02[a]
Three; *n* families (%)	23 (56)	25 (61)	48 (59)	
Four; *n* families (%)	0	5 (12)	5 (6)	

[a]*P*-value < 0.05; [b]*P*-value < 0.01.

materials given at the end of this article). Disease had manifested in approximately 19% of *SDHB* participants at any timepoint, which is similar to reported disease penetrance in the literature (Benn *et al.* 2018, Rijken *et al.* 2018). In the validation cohort, most families (61%) were represented by three generations and most nuclear families had two or three offspring (biological children.)

The transmission ratio for *SDHB* PV was 0.59 ($P = 0.005$) in the discovery cohort (Table 3), 0.67 ($P < 0.001$) in the validation cohort, and 0.63 ($P < 0.001$) in the combined

Table 3 Transmission ratio in *SDHB* families in the discovery cohort.

	Actual (95% CI)	**Expected**	***P*-value**
Cohort that underwent genetic testing ($n = 260$)	0.59 (0.53–0.65)	0.50	0.005[b]
Probands excluded ($n = 228$)	0.53 (0.46–0.60)	0.50	0.40
Cohort with complete family size data ($n = 30$)	0.63 (0.44–0.80)	0.50	0.20
Cohort excluding those <20 years of age without genetic test ($n = 269$)	0.57 (0.51–0.63)	0.50	0.03[a]
Paternal inheritance ($n = 123$)	0.62 (0.53–0.70)	0.50	0.01[a]
Maternal inheritance ($n = 124$)	0.57 (0.47–0.65)	0.50	0.18
Loss of function pathogenic variant ($n = 157$)	0.59 (0.51–0.67)	0.50	0.03[a]
Missense pathogenic variant ($n = 103$)	0.58 (0.48–0.68)	0.50	0.12
Pathogenic variant in exons 1–3 or intronic region up to IVS3 ($n = 193$)	0.59 (0.52–0.66)	0.50	0.01[a]
Pathogenic variant in exons 4–8 or intronic region from IVS3 to IVS6 ($n = 60$)	0.57 (0.43–0.69)	0.50	0.37
Male sex ($n = 125$)	0.59 (0.51–0.68)	0.50	0.04[a]
Female sex ($n = 135$)	0.58 (0.49–0.67)	0.50	0.06
Second generation ($n = 156$)	0.64 (0.56–0.72)	0.50	<0.001[b]
Third generation ($n = 104$)	0.51 (0.41–0.61)	0.50	0.92
Birth order first[c] ($n = 13$)	0.69 (0.39–0.91)	0.50	0.27
Birth order second[c] ($n = 10$)	0.60 (0.26–0.89)	0.50	0.75
Birth order third or later[c] ($n = 6$)	0.50 (0.12–0.88)	0.50	1.0
Family size one child[c] ($n = 1$)	1.0 (0.25–1.0)	0.50	1.0
Family size two children[c] ($n = 12$)	0.58 (0.28–0.85)	0.50	0.77
Family size three or more children[c] ($n = 17$)	0.65 (0.38–0.86)	0.50	0.33

[a]*P*-value < 0.05; [b]*P*-value < 0.01; [c]Analysis in families with complete family size data.

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Table 4 Transmission ratio in *SDHB* families in the combined cohort.

	Actual (95% CI)	**Expected**	***P*-value**
Cohort that underwent genetic testing ($n = 503$)	0.63 (0.58–0.67)	0.50	<0.001[b]
Probands excluded ($n = 446$)	0.58 (0.53–0.63)	0.50	<0.001[b]
Cohort with complete family size data ($n = 273$)	0.67 (0.61–0.72)	0.50	<0.001[b]
Cohort excluding those < 20 years of age without genetic test ($n = 539$)	0.59 (0.54–0.63)	0.50	<0.001[b]
Paternal inheritance ($n = 234$)	0.64 (0.57–0.70)	0.50	<0.001[b]
Maternal inheritance ($n = 252$)	0.64 (0.57–0.69)	0.50	<0.001[b]
Loss of function pathogenic variant ($n = 297$)	0.66 (0.60–0.71)	0.50	<0.001[b]
Missense pathogenic variant ($n = 206$)	0.59 (0.52–0.66)	0.50	0.02[a]
Pathogenic variant in exons 1–3 or intronic region up to IVS3 ($n = 344$)	0.63 (0.58–0.68)	0.50	<0.001[b]
Pathogenic variant in exons 4–8 or intronic region from IVS3 to IVS6 ($n = 152$)	0.62 (0.54–0.70)	0.50	0.005[b]
Male sex ($n = 236$)	0.66 (0.59–0.72)	0.50	<0.001[b]
Female sex ($n = 264$)	0.60 (0.54–0.66)	0.50	0.001[b]
Second generation ($n = 294$)	0.66 (0.60–0.71)	0.50	<0.001[b]
Third generation ($n = 194$)	0.60 (0.53–0.67)	0.50	0.005[b]
Birth order first[c] ($n = 110$)	0.75 (0.65–0.82)	0.50	<0.001[b]
Birth order second[c] ($n = 90$)	0.67 (0.60–0.76)	0.50	0.002b
Birth order third or later[c] ($n = 56$)	0.55 (0.42–0.69)	0.50	0.50
Family size one child[c] ($n = 15$)	1.00 (0.78–1.00)	0.50	<0.001[b]
Family size two children[c] ($n = 112$)	0.72 (0.63–0.80)	0.50	<0.001[b]
Family size three or more children[c] ($n = 146$)	0.59 (0.51–0.67)	0.50	0.004[b]

[a]*P*-value < 0.05; [b]*P*-value < 0.01; [c]Analysis in families with complete family size data.

cohort (Table 4 and Fig. 2). For the discovery cohort, TRD was apparent when analysing for each of paternal inheritance, loss of function PV, mutation within the proximal region of the gene (exons 1–3 and up to IVS3), male sex, and the second generation from the proband (Table 3). No parent-of-origin effect was observed in the combined cohort. TRD remained significant after adjusting for potential confounders: 0.67 ($P < 0.001$) if families with incomplete family size data were excluded and 0.58 ($P < 0.001$) if probands were excluded. Of the

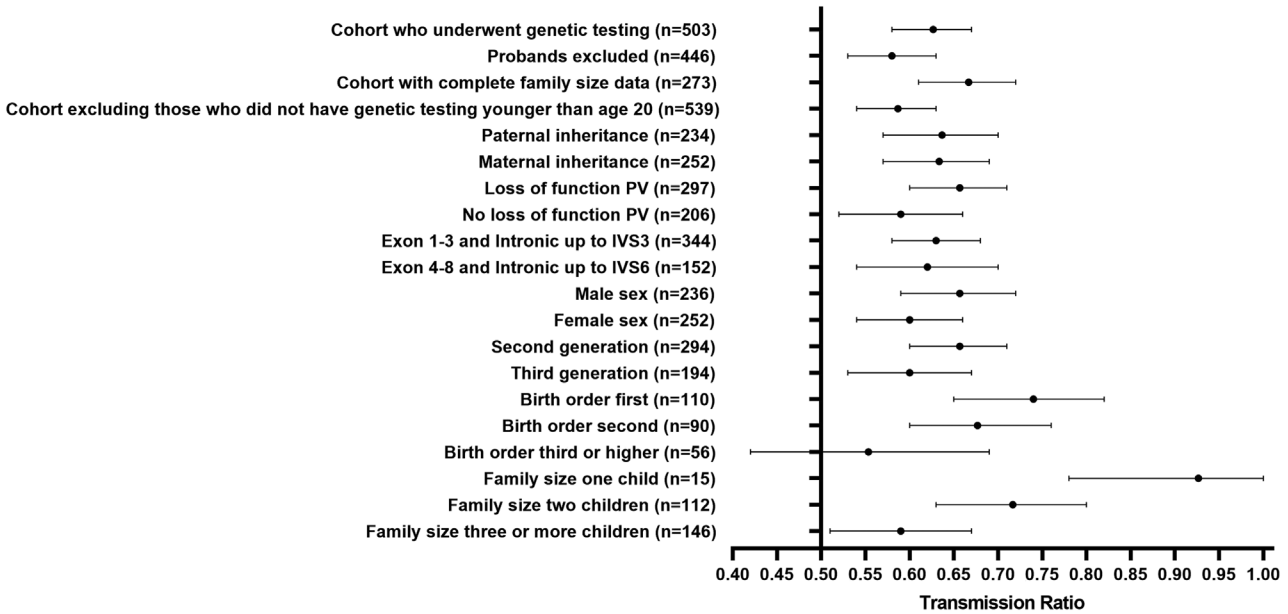

Figure 2
Forest plot of transmission ratio in *SDHB* families in the combined cohort.

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Table 5 Generalized linear model with binary logistic regression of predictors of TRD in the combined cohort of participants that underwent genetic testing ($n = 503$).

Predictors of TRD	***P*-value**	**OR** (95% CI)
Male	0.41	0.85 (0.69–1.24)
Loss of function pathogenic variant	0.21	1.29 (0.87–1.91)
PV in exons 1–3 or intronic region up to IVS3	0.79	0.94 (0.62–1.44)
Paternal inheritance	0.96	0.99 (0.68–1.44)
Test	***P*-value**	χ^2
Overall model likelihood ratio test (omnibus test)	0.99	2.39

72 individuals who did not have genetic testing, 36 were younger than 20 years of age; after excluding these participants, the transmission ratio was 0.59 ($P < 0.001$). No factors predicted TRD on a generalized linear model with binary logistic regression (Tables 5 and 6).

Transmission ratio analysis was replicated for the *SDHD* cohort at St Bartholomew's Hospital: 81 patients from 13 families, most commonly of 3 generations (range 2–4) and with 2 children per nuclear family (range 1–5) (Table 7). Phenotype expression was dependent on paternal inheritance, as expected. Of the 61 participants with confirmed germline testing, 43 harboured an *SDHD* PV (Supplementary Table 2), which represents a significant distortion in transmission ratio: 0.70 ($P = 0.0019$). TRD in *SDHD* was upheld even when assuming that a Mendelian 50% of those with unknown genotypes were carriers (0.65, $P = 0.0073$). Neither clinical centre had *SDHA* or *SDHC* cohorts of sufficient size for analysis.

Discussion

A TRD of 60% in favour of the *SDHB* PV being transmitted was evident in our cohort. In the discovery cohort, it appeared that TRD was associated with particular variables, but the analysis was limited by incomplete family data and insufficient power. In the combined cohort, TRD was observed irrespective of sex, parent of origin, loss of function PV, or location of the mutation within the proximal or distal region of the gene. Given that rates of genetic testing differed between centres, we assessed complete family data. When families with incomplete family size data were excluded, TRD was still noted. When probands were excluded, TRD still occurred, suggesting TRD was not due to oversampling of cases (Gemechu *et al.* 2020). We considered the possibility of bias in young individuals not undergoing genetic testing due to being asymptomatic since the median age of disease diagnosis is 37 years (Davidoff *et al.* 2022), but after the exclusion of participants younger than age 20 years without a genetic test, TRD was still observed. Birth order third or later was not associated with TRD, likely due to insufficient power ($n = 56$), given that heterogeneity was absent on Levene's test. As TRD was consistently observed across different variables, the finding that no particular factors predicted TRD on the generalized linear model was unsurprising.

The 60% distortion in transmission of pathogenic *SDHB* alleles is consistent with the magnitude of other examples of TRD: PVs of the tumour suppressor gene for retinoblastoma, *RB-1,* were found to have 63% transmission from affected males to sons (Naumova & Sapienza 1994); *STX16-GNAS* mutations in autosomal dominant pseudohypoparathyroidism type Ib were transmitted to 63% of offspring (Kiuchi *et al.* 2021); mutated alleles in long-QT syndrome conferred 55% transmission to female offspring (Imboden *et al.* 2006); and a study of embryos

Table 6 Generalized linear model with binary logistic regression of potential predictors of TRD in the combined cohort of families with complete family size data ($n = 273$).

Predictors of TRD	***P*-value**	**OR** (95% CI)
Male	0.23	0.71 (0.41–1.24)
Loss of function pathogenic variant	0.06	1.73 (0.97–3.11)
PV in exons 1–3 or intronic region up to IVS3	0.83	0.93 (0.49–1.78)
Paternal inheritance	0.99	1.00 (0.56–1.80)
Birth order	0.67	1.06 (0.80–1.41)
Family size (number of children)	0.37	1.10 (0.88–1.41)
Test	***P*-value**	χ^2
Overall model likelihood ratio test (omnibus test)	0.12	10.05

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Table 7 Baseline characteristics of the *SDHD* cohort.

SDHD* cohort, *n	**81**
Male, *n* (%)	45 (57)
Probands, *n* (%	13 (16)
Genetic testing, *n* (%)	61 (75)
Loss of function pathogenic variant, *n* (%)	18 (22)
Birth order	
First, *n* (%)	39 (48)
Second, *n* (%)	25 (31)
Third or later, *n* (%)	17 (21)
Family size: children	
One, *n* (%)	10 (12)
Two, *n* (%)	14 (17)
Three or more, *n* (%)	9 (11)
Family size: generations analysed	
Two, *n* (%)	41 (51) from 8 families
Three, *n* (%)	25 (31) from 3 families
Four, *n* (%)	15 (18) from 2 families

from preimplantation genetic testing for myotonic dystrophy type 1 found that 59% harboured the CTG nucleotide repeat expansion (Dean *et al.* 2006).

It has been suggested that the phenomenon of anticipation is apparent in *SDH*-deficient disease (Antonio *et al.* 2020), albeit without a trinucleotide repeat expansion to facilitate this in a classical way. Whilst an earlier age of tumour diagnosis was documented in some subsequent generations, this was attributed to an early age of screening and surveillance; furthermore, this phenomenon was not borne out across our 82 families to suggest a genuine pattern of an underlying biological change in disease penetrance across the generations.

Limitations to this study included some uncollected data that could hypothetically influence the interpretation of inheritance patterns, such as age of parenthood, miscarriage rate, and birth order. The sample size was robust relative to accessible cohorts of rare disease but may limit extrapolation from statistical significance to biological significance, such as with the question of a parent-of-origin effect on transmission. However, to counter potential sources of bias, we tested the sensitivity of our results by excluding, in turn, possible confounders: families with incomplete family size data, probands, and untested participants less than 20 years old. None of these analyses significantly altered the main finding of TRD in favour of *SDHB* PVs.

The reason for a TRD in *SDH-B* and *-D* is unknown. We hypothesize the mechanism could occur at the post-fertilization stage and arise as a selective advantage, perhaps for adapting to hypoxia; however, assessing the timing and mechanisms for TRD was beyond the scope of the present study. It is fascinating to consider how an embryonic survival advantage for hypoxia/pseudo-hypoxia might then be accompanied by variably penetrant tumour risk in postnatal life. Intriguingly, several tumour suppressor genes and oncogenes have also been demonstrated to manifest TRD in favour of the mutant allele (Huang *et al.* 2013), including *CDKN1C* (Sazhenova & Lebedev 2008), *HRAS1*, and *SIRT3* (De Rango *et al.* 2008). Moreover, *CDKN1C* has been implicated in the pathogenicity of *SDHAF2* and *SDHD* mutations when arising from loss of maternal chromosome 11 (Hoekstra *et al.* 2017), whereas HRAS and sirtuin-3 both regulate mitochondrial function (Dard *et al.* 2022, Papa & Germain 2014).

The clinical relevance of distortion in the transmission of *SDH-B* and *-D* mutations is immediately apparent: a TRD that favours the potential for tumourigenesis has significant implications for genetic counselling of all carriers. The role of pre-implantation genetic diagnosis is arguably stronger when the odds are against the likelihood of healthy offspring. We encourage other centres to analyse their cohorts similarly to validate our findings, with a view to updating guidelines on genetic counselling. An understanding of the mechanism behind TRD in *SDH*, where the heterozygous state may have an advantage, might lead to insights that later allow interventions in carriers to decrease the risk of tumour development.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/ERC-22-0233.

Declaration of interest

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Author contribution statement

S A Akker and R J Clifton-Bligh authors are Senior co-authors. Conceptualization: RCB; Data curation: DFD, ESL, DEB, YS, ED, JRB; Formal analysis: DFD, ESL, ED; Writing – original draft: DFD, ESL; Writing – review & editing: RCB, SAA

References

Antonio K, Valdez MMN, Mercado-Asis L, Taïeb D & Pacak K 2020 Pheochromocytoma/paraganglioma: recent updates in genetics, biochemistry, immunohistochemistry, metabolomics, imaging and therapeutic options. *Gland Surgery* **9** 105–123. (https://doi.org/10.21037/gs.2019.10.25)

Benn DE, Zhu Y, Andrews KA, Wilding M, Duncan EL, Dwight T, Tothill RW, Burgess J, Crook A, Gill AJ, *et al.* 2018 Bayesian approach to determining penetrance of pathogenic SDH variants. *Journal of Medical Genetics* **55** 729–734. (https://doi.org/10.1136/jmedgenet-2018-105427)

Bettencourt C, Fialho RN, Santos C, Montiel R, Bruges-Armas J, Maciel P & Lima M 2008 Segregation distortion of wild-type alleles at the Machado-Joseph disease locus: a study in normal families from the Azores islands (Portugal). *Journal of Human Genetics* **53** 333–339. (https://doi.org/10.1007/s10038-008-0261-7)

Dahia PL 2014 Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity. *Nature Reviews. Cancer* **14** 108–119. (https://doi.org/10.1038/nrc3648)

Dard L, Hubert C, Esteves P, Blanchard W, Bou About G, Baldasseroni L, Dumon E, Angelini C, Delourme M, Guyonnet-Dupérat V, *et al.* 2022 HRAS germline mutations impair LKB1/AMPK signaling and mitochondrial homeostasis in Costello syndrome models. *Journal of Clinical Investigation* **132** e131053. (https://doi.org/10.1172/JCI131053)

Davidoff DF, Benn DE, Field M, Crook A, Robinson BG, Tucker K, De Abreu Lourenco R, Burgess JR & Clifton-Bligh RJ 2022 Surveillance improves outcomes for carriers of SDHB pathogenic variants: A multicenter study. *Journal of Clinical Endocrinology and Metabolism* **107** e1907–e1916. (https://doi.org/10.1210/clinem/dgac019)

De Rango F, Dato S, Bellizzi D, Rose G, Marzi E, Cavallone L, Franceschi C, Skytthe A, Jeune B, Cournil A, *et al.* 2008 A novel sampling design to explore gene-longevity associations: the ECHA study. *European Journal of Human Genetics* **16** 236–242. (https://doi.org/10.1038/sj.ejhg.5201950)

Dean NL, Loredo-Osti JC, Fujiwara TM, Morgan K, Tan SL, Naumova AK & Ao A 2006 Transmission ratio distortion in the myotonic dystrophy locus in human preimplantation embryos. *European Journal of Human Genetics* **14** 299–306. (https://doi.org/10.1038/sj.ejhg.5201559)

Gemechu SD, Van Vliet CM, Win AK, Figueiredo JC, Le Marchand L, Gallinger S, Newcomb PA, Hopper JL, Lindor NM, Jenkins MA, *et al.* 2020 Do the risks of Lynch syndrome-related cancers depend on the parent of origin of the mutation? *Familial Cancer* **19** 215–222. (https://doi.org/10.1007/s10689-020-00167-4)

Hoekstra AS, Hensen EF, Jordanova ES, Korpershoek E, Van Der Horst-Schrivers AN, Cornelisse C, Corssmit EP, Hes FJ, Jansen JC, Kunst HP, *et al.* 2017 Loss of maternal chromosome 11 is a signature event in SDHAF2, SDHD, and VHL-related paragangliomas, but less significant in SDHB-related paragangliomas. *Oncotarget* **8** 14525–14536. (https://doi.org/10.18632/oncotarget.14649)

Huang LO, Labbe A & Infante-Rivard C 2013 Transmission ratio distortion: review of concept and implications for genetic association studies. *Human Genetics* **132** 245–263. (https://doi.org/10.1007/s00439-012-1257-0)

Imboden M, Swan H, Denjoy I, Van Langen IM, Latinen-Forsblom PJ, Napolitano C, Fressart V, Breithardt G, Berthet M, Priori S, *et al.* 2006 Female predominance and transmission distortion in the long-QT syndrome. *New England Journal of Medicine* **355** 2744–2751. (https://doi.org/10.1056/NEJMoa042786)

Infante-Rivard C & Weinberg CR 2005 Parent-of-origin transmission of thrombophilic alleles to intrauterine growth-restricted newborns and transmission-ratio distortion in unaffected newborns. *American Journal of Epidemiology* **162** 891–897. (https://doi.org/10.1093/aje/kwi293)

Kiuchi Z, Reyes M & Jüppner H 2021 Preferential maternal transmission of STX16-GNAS mutations responsible for autosomal dominant pseudohypoparathyroidism type Ib (PHP1B): another example of transmission ratio distortion. *Journal of Bone and Mineral Research* **36** 696–703. (https://doi.org/10.1002/jbmr.4221)

Naumova A & Sapienza C 1994 The genetics of retinoblastoma, revisited. *American Journal of Human Genetics* **54** 264–273.

Nölting S, Bechmann N, Taieb D, Beuschlein F, Fassnacht M, Kroiss M, Eisenhofer G, Grossman A & Pacak K 2022 Personalized management of pheochromocytoma and paraganglioma. *Endocrine Reviews* **43** 199–239. (https://doi.org/10.1210/endrev/bnab019)

Papa L & Germain D 2014 SirT3 regulates the mitochondrial unfolded protein response. *Molecular and Cellular Biology* **34** 699–710. (https://doi.org/10.1128/MCB.01337-13)

Pardo-Manuel De Villena F, De La Casa-Esperon E, Briscoe TL & Sapienza C 2000 A genetic test to determine the origin of maternal transmission ratio distortion. Meiotic drive at the mouse Om locus. *Genetics* **154** 333–342. (https://doi.org/10.1093/genetics/154.1.333)

Riess O, Epplen JT, Amoiridis G, Przuntek H & Schöls L 1997 Transmission distortion of the mutant alleles in spinocerebellar ataxia. *Human Genetics* **99** 282–284. (https://doi.org/10.1007/s004390050355)

Rijken JA, Niemeijer ND, Jonker MA, Eijkelenkamp K, Jansen JC, Van Berkel A, Timmers HJLM, Kunst HPM, Bisschop PHLT, Kerstens MN, *et al.* 2018 The penetrance of paraganglioma and pheochromocytoma in SDHB germline mutation carriers. *Clinical Genetics* **93** 60–66. (https://doi.org/10.1111/cge.13055)

Sazhenova EA & Lebedev IN 2008 Epimutations of the KCNQ1OT1 imprinting center of chromosome 11 in early human embryo lethality. *Genetika* **44** 1609–1616. (https://doi.org/10.1134/s1022795408120028)

Tufton N, Sahdev A, Drake WM & Akker SA 2019 Can subunit-specific phenotypes guide surveillance imaging decisions in asymptomatic SDH mutation carriers? *Clinical Endocrinology* **90** 31–46. (https://doi.org/10.1111/cen.13877)

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