The Molecular Causes Of Congenital Hypothyroidism: The Scottish Experience.

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Introduction:

Congenital hypothyroidism (CH): 1:3000 to 1:4000 newborns

- **Thyroid dysgenesis (TD):80-85%**
  - Sporadic disease,
  - 2-5% : genetic origin.
- **Thyroid Dyshormonogenesis: DHG: 15-20%**
- Inherited forms of congenital hypothyroidism (CH) account for approximately one quarter of all causes of CH. These include biosynthetic defects and developmental and morphological abnormalities.

Objective: Describe the Scottish experience of genetic testing in CH.

Methods:

- Retrospective study from August 1979 to March 2016 (37 years).
- Patients were selected on the basis of imaging findings or strong family history of CH.
- 3 genes tested in Glasgow: Thyroperoxidase gene TPO, TSH receptor gene TSHR, Thyroglobulin gene Tg.
- 4 genes tested in Germany Mainz: THOX2, NIS, DUOXA2, PAX8.

Results and Conclusions:

- Of 970 infants referred by Scottish neonatal screening, 649 cases of permanent CH were identified. Infants who were unwell, premature or had dysmorphic features were excluded.
- 512/649 (79%) had thyroid dysgenesis and remaining 137/649 (21%) had thyroid dyshormonogenesis.
- 66/137 cases of suspected dyshormonogenesis had genetic testing 44 of whom had available results.
- 28/44 (64%; M:F 12:16) had a mutation or variant found.
- 4/28 (14.3%) of cases where a mutation or variant were found were associated with a congenital cardiac abnormality, and 2/28 (7%) were associated with Down's syndrome; one PAX8, one TSHR.
- 18/28 (64.3%) had a first degree relative with thyroid disease compared with only 25% in patients with no detected mutation.
- Among patients with mutations there were 5 kindreds accounting for 11/26 individual patients.
- There were two cases of familial dysgenesis (one aplasia and one ectopia).
- Mutations were identified in (Tg) n= 10(36%), TPO n=8(29%), TSHR n=4(14%), PAX8 n=2(7%), and THOX2 n=2(7%) genes. Two patients (7%) had TPO sequence variants, one with heterozygous Tg gene mutation.
- No significant difference was found between biochemical results at assessment for infants with TPO and Tg gene mutations; the median (range) TSH, fT4 and quantitative Tg values were 100 (21.9-385) vs 150 (7.17-401) mU/L (p=0.5); 5.45 (1.8-15.8) vs 7.45 (3.8-11.6) pmol/L (p=0.3); and 160(<2.0-2993) vs 5 (<2.0-3977) ug/l(p=0.2) respectively.
- On ultrasound, where available, patients with TPO mutation had normal or small glands whereas 80% of Tg gene mutations had remarkably large glands.
- **Conclusion:** Thyroid test results don't appear to be helpful for selecting patients for genetic analysis nor for targeting mutation analysis. However thyroid imaging could be useful for targeting mutation analysis as patients with Tg mutation had markedly large glands.

References:
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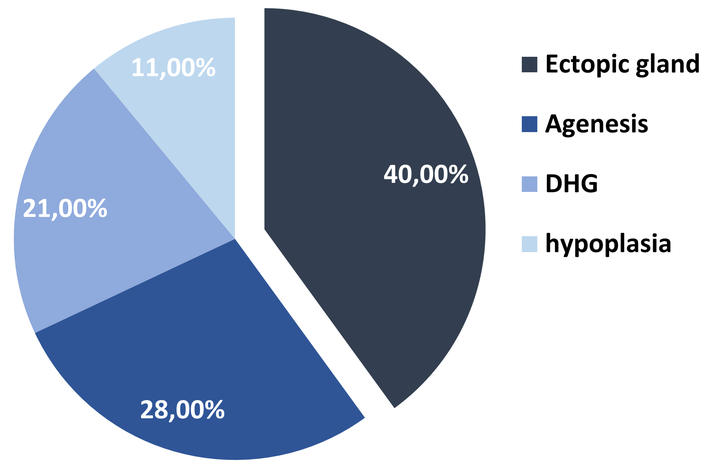

Figure1: Distribution of 649 patients with true CH according to the aetiology

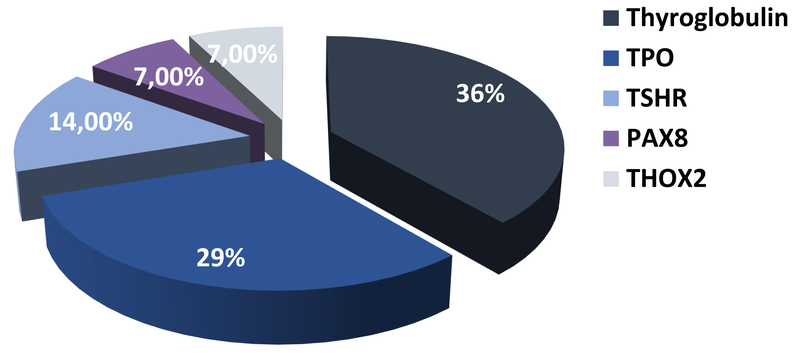

Figure3: Mutation types in 26 patients with positive mutations

	Patients with mutation n=28	Patients without mutation n=16	p value
Familial history of thyroid disease	n=18(64.3%)	n=4 (25%)	**p=0.005**
Maternal history of thyroid disease	n=7 (25%)	n=4 (25%)	p=0.8
Median (range) Maternal age at birth	30 (17-38)	25 (19-49)	p=0.25
Median (range) Paternal age at birth	31 (21-52)	31 (21-48)	p=0.4
Dysmorphic	n=2 (7%) Down syndrome (PAX8, TSHR)	No	
Congenital abnormalities	n=4 (14.3%) cardiac abnormality Plagiocephaly	No	
M/F	12/16: 0.75	7/9 0.77	
Median (range) fT4 (pmol/l)	8.1 (1.79-26.9)	7 (2.9-24)	p=0.6
Median (range) TSH	150 (7.17-385)	100.1 (23-850)	p=0.6
Imaging	Enlarged n=12 (52%) Normal n=4 (18%) Hypoplasia n=5(22%) Agenesis n=1 (4%) Nodular n=1 (4%)	Athyreosis n=4 (25%) Enlarged n=4 (25%) Ectopic n=4 (25%) Normal n=2 (12.5%)	

Table1: Comparison between characteristics of patients with positive mutations and patients without mutations

Mutation	TPO n=8	Tg n=10	p value	TSHR n=4	PAX8 n=2
M/F	3/4: 0.75	4/7: 0.57		2 boys	1/1: 1
Dysmorphic	0	0			
Congenital abnormalities/ other	Cardiac abnormality/ plagiocephaly, Perthe disease	0		1 patient with Cardiac abnormality and down syndrome	1 patient with Cardiac abnormality and down syndrome
Median (range) fT4 (pmol/l)	5.45(1.8-15.8)	7.45 (3.8-11.6)	p=0.3	7.4 (4-10.8)	12.65 (10.2 - 15.1)
Median (range) TSH	100 (21.9-385)	150 (7.17-401)	p=0.5	320.5 (269.86-371.43)	>150 (1 patient)
Median (range) Tg	160 (<2-2993)	5 (<2- 3977)	p=0.2	Done in 1 patient = 32	73 (43-103)
Imaging	Normal n=2 (25%) Small n=2 (25%) No data n=2 (25%) Large n=1 (12.5%)	Very Large n=8(80%) Normal n=1 (10%) Small n=1 (10%)		Aplasia n=1 (50%) Small n=1 (50%)	Large n=1 (50%) Small n=1 (50%)

Table2: Comparison of Characteristics of patients according to mutations

55ESPE 890--P1
Thyroid
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DOI: 10.3252/pso.eu.55ESPE.2016
Poster presented at: ESPE 2016 PARIS