Maternal uniparental disomy for chromosome 20: physical and endocrinological characteristics of six patients

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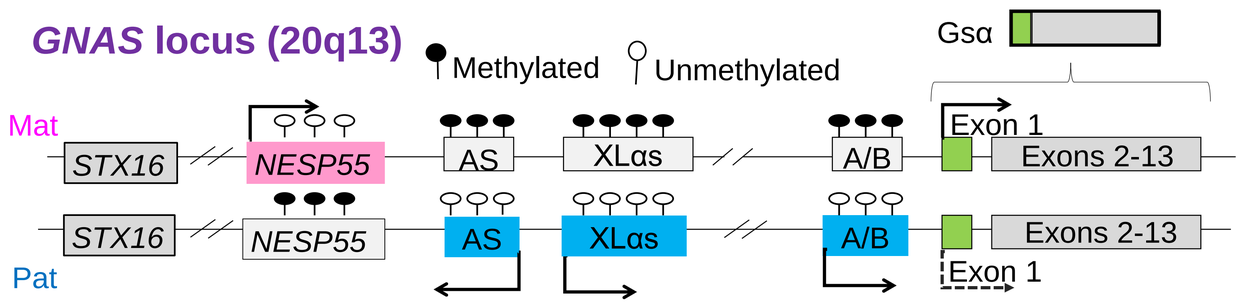
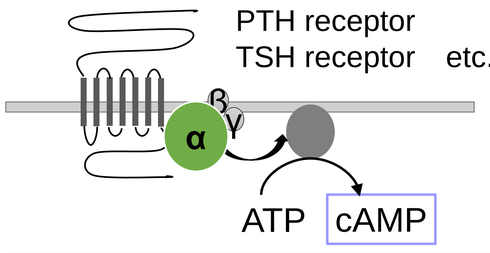
Introduction and objectives

GNAS locus (20q13)





Gsα is expressed predominantly from the maternally allele in the proximal tubule, thyroid, pituitary and ovary.

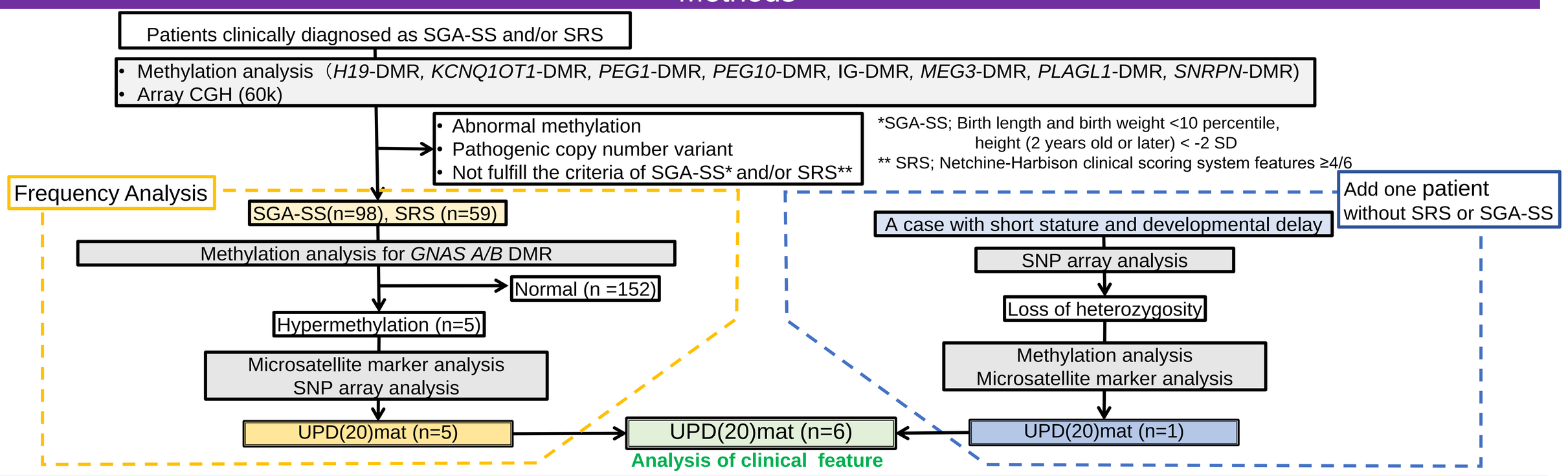
UPD(20)mat

- Maternal uniparental disomy for chromosome 20 (UPD(20)mat) is a poorly characterized condition. Only 10 non-mosaic cases have been studied clinically[1) 2)].
- The phenotype of these cases overlapped with that of Silver-Russell syndrome (SRS) and small for gestational age-short stature (SGA-SS); however, the etiological relationship between UPD(20)mat and SRS/SGA-SS remains unclear.
- The symptoms of UPD(20)mat may be related to over expression of Gsα and decreased expression of paternally expressed gene.
- No report has described endocrinological assessment of UPD(20)mat patients.

Objectives

- To clarify the frequency of UPD(20)mat in patients with SRS and/or SGA-SS without known genetic causes
- To clarify clinical features of UPD(20)mat.

Methods



Results

Frequency

Four patients (6.7%) with UPD(20)mat were identified among 59 patients with SRS without known genetic causes.
One patint (1.0%) with UPD(20)mat was identified among 98 patients with SGA-SS without known genetic causes.

Clinical features

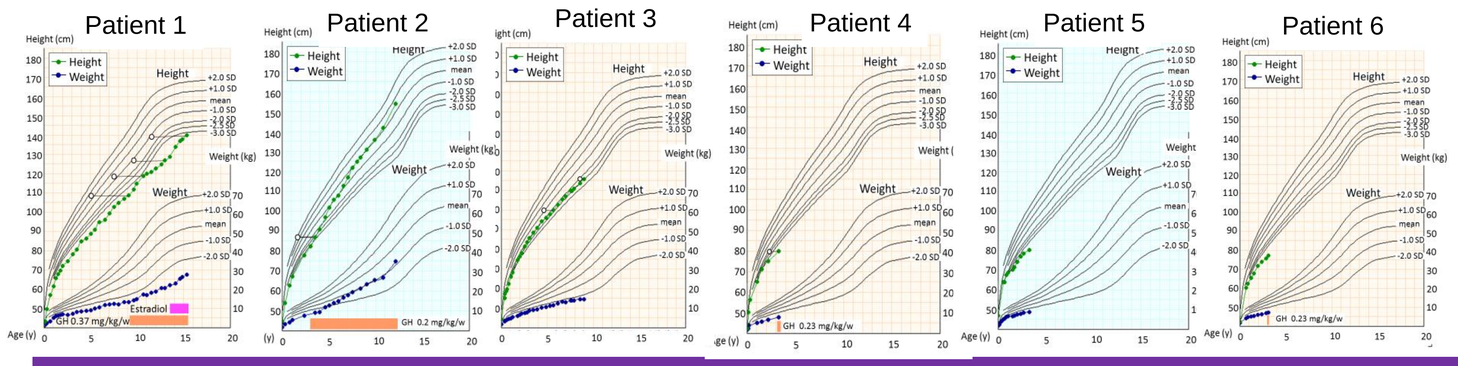
Patient	1	2	3	4	5	6
Sex	F	M	F	F	M	F
Age at last evaluation (y:m)	14 : 10	12 : 1	8 : 11	3:3	3:3	3:1
Birth length SDS	–2.7	–1.6	–1.4	–2.3	0.2	–2.6
Birth weight SDS	–4.1	–2.8	–1.9	–2.2	–1.5	–2.4
Birth OFC SDS	–1.7	–1.1	–1.9	–1.2	–1.2	–0.8
Present height SDS	–3.5	0.6	–2.5	–4.0	–4.1	–3.6
Present weight SDS	–3.1	–0.8	–2.4	–3.3	–3.1	–3.9
Height SDS at start of GH therapy	–3.7	–3.0	–	–4.0	–	–3.6
NH-CSS *	4	5	4	3	3	5
Feeding difficulty	+	–	+	+	+	+
Tube feeding or gastrostoma	gastrostoma (~10y)	–	–	tube feeding	–	–
Hypotonia	–	–	–	+	+	+
Developmental delay	+	–	–	+	+	+

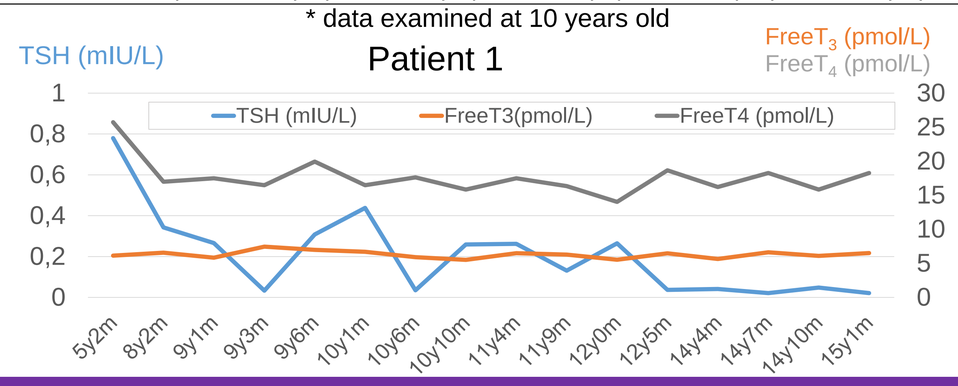
*NH-CSS; Netchine-Harbison clinical scoring system. SRS ≥ 4 out of 6 NH-CSS criteria.

Endocrinological features

Patient	1	2	3	4	5	6
Age at examination (y:m)	15:1	12:1	8:11	3:3	2:8	3:0
Calcium (mmol/L)	2.37 (2.17–2.55)	2.42 (2.17–2.55)	2.47 (2.17–2.55)	2.74 (2.20–2.65)	2.67 (2.20–2.65)	2.47 (2.20–2.65)
Inorganic phosphate (mmol/L)	1.23 (0.90–1.86)	1.87 (1.22–1.99)	1.48 (1.22–1.99)	1.54 (1.22–1.99)	1.67 (1.22–1.99)	1.36 (1.22–1.99)
Intact PTH (pmol/L)	3.7 (1.5–8.3)	4.3* (1.5–8.3)	1.8 (1.5–8.3)	1.1 (1.5–8.3)	2.4 (1.5–8.3)	3.1 (1.5–8.3)
1,25 $(OH)_2$ vitamin D (pmol/L)	157 (48–167)	145 * (48–167)	88 (48–167)	175 (48–167)	79 (48–167)	119 (48–167)
TSH (mIU/L)	<0.02 (0.4–4.0)	0.69 (0.4–4.0)	0.63 (0.4–4.0)	1.80 (0.4–4.0)	1.31 (0.4–4.0)	0.74 (0.4–4.0)
Free T_3 (pmol/L)	5.8 (3.5–6.7)	7.8 (3.9–7.4)	5.0 (3.9–7.0)	7.2 (3.4–6.7)	6.0 (3.5–7.1)	6.6 (3.4–6.7)
Free T_4 (pmol/L)	17.5 (12.2–23.6)	11.6 (11.6–25.1)	18.2 (13.4–25.9)	18.0 (13.0–25.1)	14.3 (12.9–25.1)	18.1 (13.0–25.1)

* data examined at 10 years old





Discussion

- Growth failure and feeding difficulty could be attributable to deficiency of paternally expressed GNAS transcripts including XLαs, because mice lacking XLαs on the paternal allele showed poor sucking and growth failure[3) 4)].
- Hypercalcemia with low or low-normal intact PTH in patients 4 and 5 can be explained by increased sensitivity of the PTH receptor due to Gsα overexpression.
- Low TSH in patient 1 may reflect TSH receptor hypersensitivity. TSH levels of patient 1 progressively decreased after 8 years of age, the hormone hypersensitivity associated with UPD(20)mat may gradually develop with age.

Conclusions

- This study suggest that UPD(20)mat underlies severe growth failure and feeding difficulties and may account for more than 6% of cases of SRS of unknown etiology, and small percentages of SGA-SS. One patient indicate that UPD(20)mat can also underlie SS without SGA.
- Most importantly, this study provides the first indication that UPD(20)mat is associated with hypersensitivity of Gsα-mediated hormone receptors, which may gradually develop with age.

References

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