

A laboratory harmonization strategy for steroid hormone profiling by MoM-transformed, normalized reference ranges independent of age-, sex - and units

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Conclusion:

Age- and sex-independent MoMs are straightforward for clinically relevant display of multisteroid patterns. In addition, defined single steroid MoMs can serve alone as predictors for 21OHD and 11OHD. Finally, MoM-transformation offers a valuable strategy of national and international routine - and scientific steroid hormone data exchange due to improved comparability.

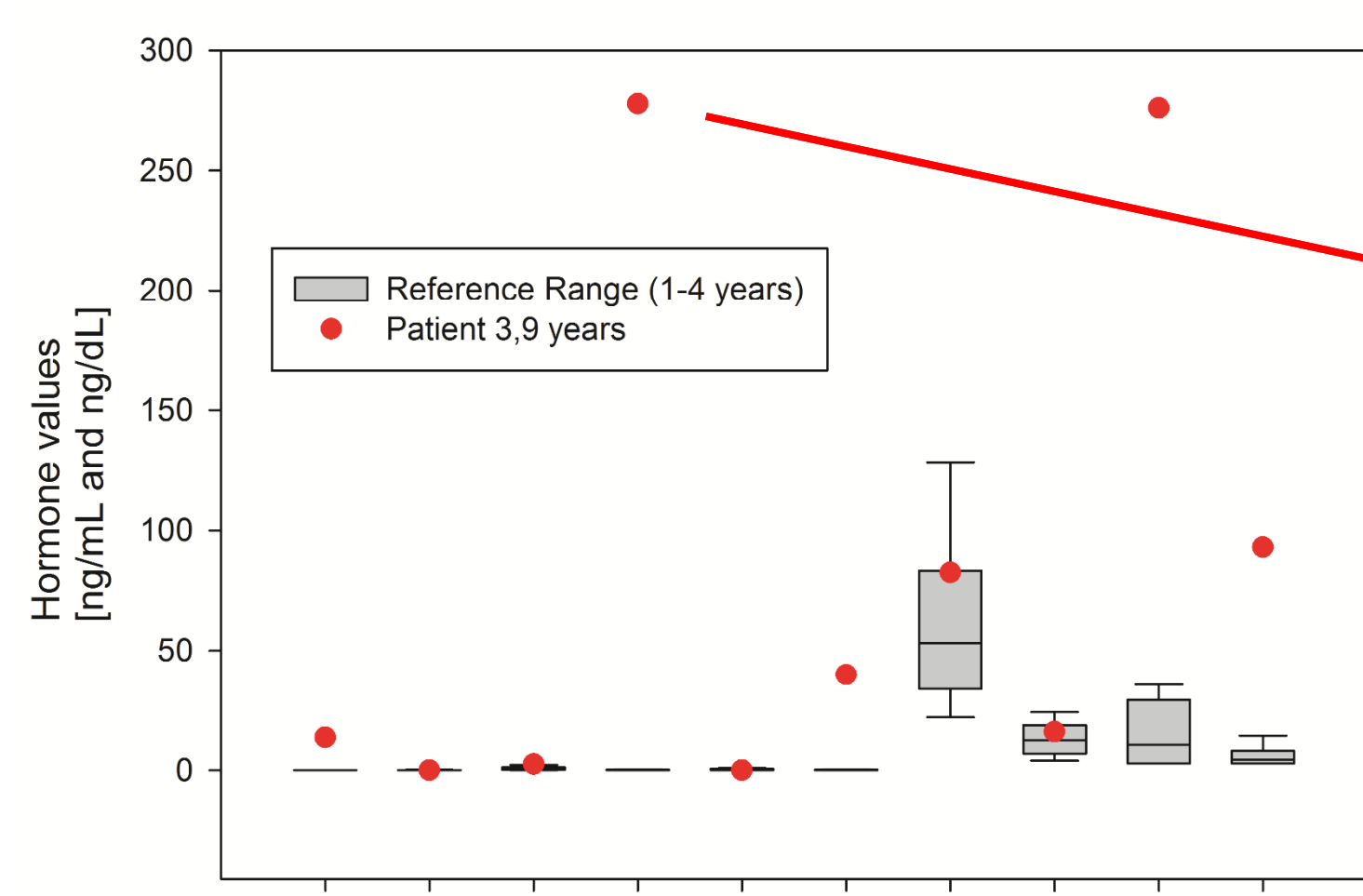
Introduction:

The high complexity of Pediatric reference ranges across age, sex and units impairs clinical application and comparability of steroid hormone data, e.g., in CAHs. We developed a Multiples-of-Median (MoM) normalization tool to overcome this major drawback in Pediatric Endocrinology.

Method and Subjects:

Multiples of Median MoM-calculation: Hormone concentrations in a given patient are divided through the median of the age- and sex-specific reference range. LC-MS/MS data comprising 10 steroid hormones representing 905 controls (555 males, 350 females, 0 to >16 years) from two previous datasets were MoM-transformed across age and sex. 24 genetically proven CAH patients were included (21OHD, N=19; 11OHD, N=5). As example, two different patients with 21OHD are chosen:

Patient 1: female, age: 3,9 years, presumed diagnosis: bone age acceleration



	Female				Male				
	Age	N	2.5%	Median	97.5%	N	2.5%	Median	97.5%
17OHP [ng/mL]	<1W	9	0.44	0.96	2.80	14	0.08	0.68	1.20
	2W-2M	25	0.32	0.66	1.29	27	0.10	0.54	1.94
	3-11M	20	0.06	0.28	0.80	31	0.06	0.42	2.15
	0-1Y	54	0.06	0.54	1.33	72	0.06	0.50	2.15
	1-6Y	99	0.06	0.19	0.57	51	0.06	0.20	0.57
	7-12Y	222	0.06	0.25	0.85	101	0.06	0.25	0.83
	13-15Y	95	0.06	0.26	0.89	60	0.06	0.35	1.16
	>16Y	86	0.06	0.30	0.85	66	0.08	0.74c	1.86

Fig. 1: Hormone values and reference range patient 1.

Table 1: Reference ranges of 17-Hydroxy-Progesterone, 17OHP, for female and males, aged 0-18 years.

Patient 2: male, age: 10 days presumed diagnosis: 21OHD because of elevated 17OHP in newborn screening

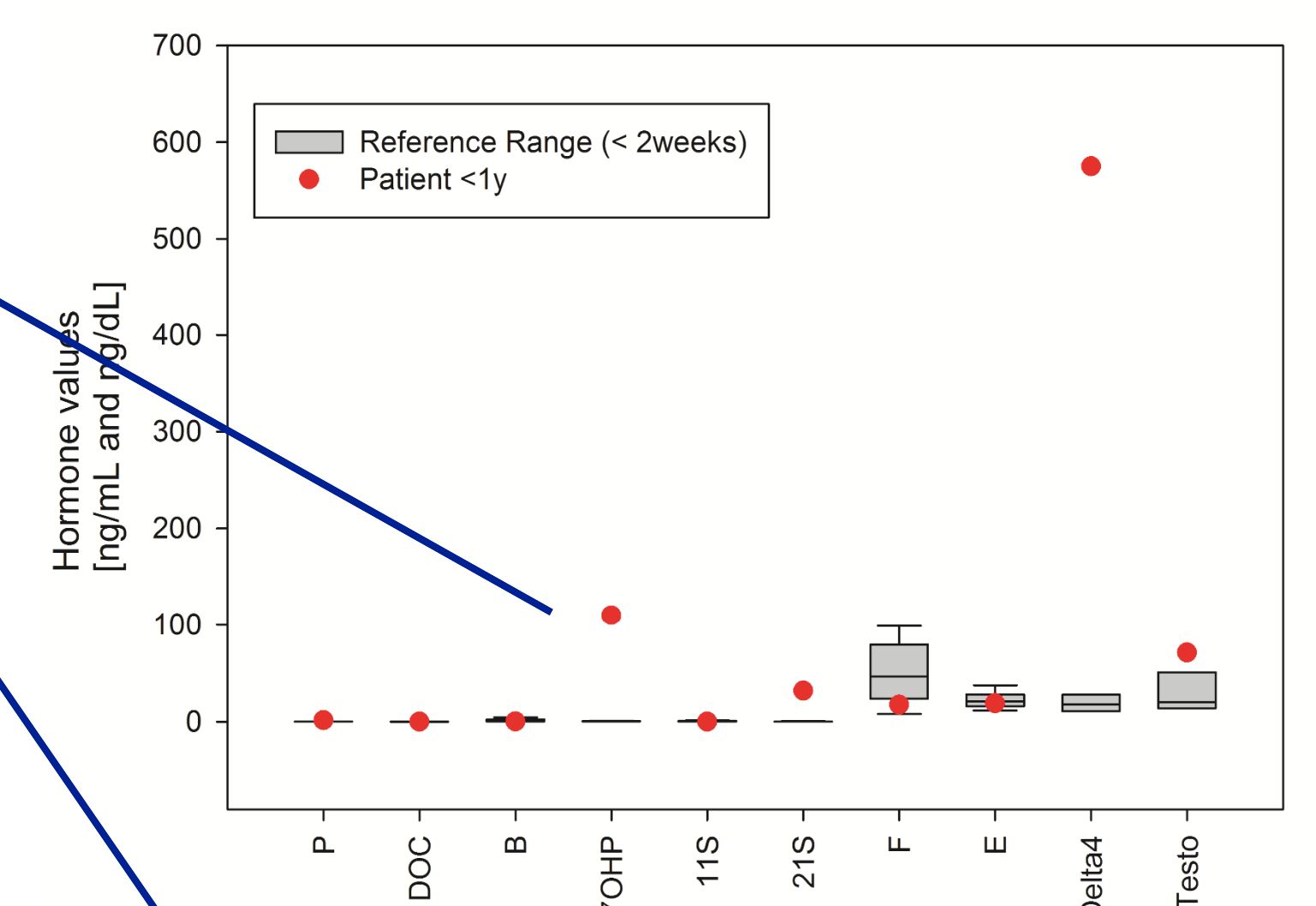


Fig. 2: Hormone values and reference range patient 2.

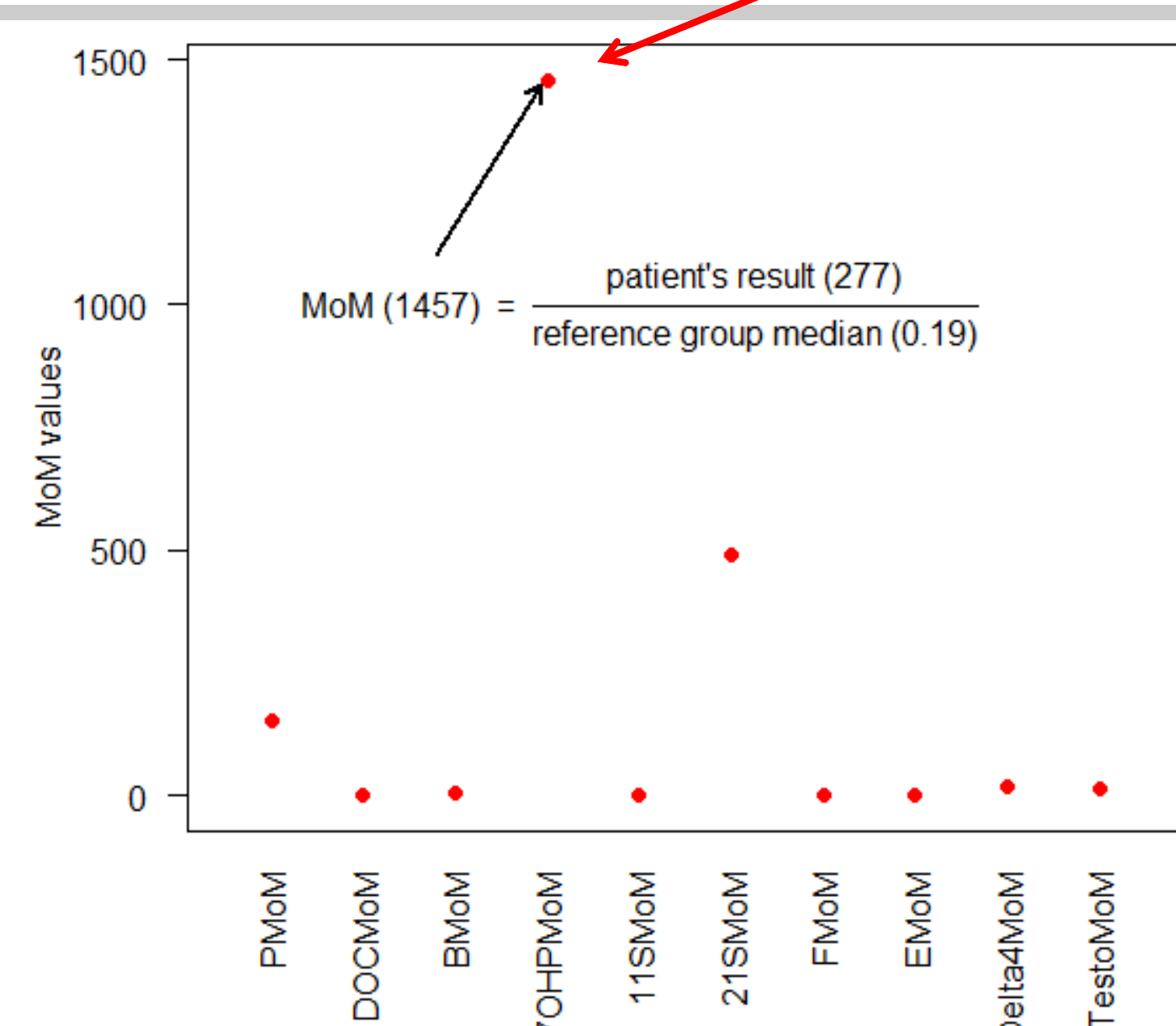


Fig. 3: MoM values of patient 1.

Results:

21OHD and 11OHD showed disease-typical MoM-patterns across the 10-steroid LC-MS/MS profile, Figure 5. In addition, MoM cut-offs for single steroids were computed for predicting 21OHD and 11OHD, respectively, Table 2.

21OHD	MoM cut-off	sensitivity [%]	specificity [%]
17OHP	>3,78	100	98,83
21S	>12,28	94,74	100
11OHD	MoM cut-off	sensitivity [%]	specificity [%]
11S	>13,18	100	100

Table 2: single steroid cut-off MoMs

The single cut-off values were validated through new, independent patients, Figure 6.

- 21OHD, N=8
- adrenal cortical carcinoma, N=6;
- obesity, N=40

Abbreviations of Hormones: P: Progesterone, DOC, Deoxycorticosterone, B, Corticosterone, 17OHP, 17-Hydroxy-Progesterone, 11S, 11Deoxycortisol, 21S, 21Deoxycortisol, F, Cortisol, E, Cortisone, Delta4, Androstenedione, Testo, Testosterone.

References:

D. Zalas *et al.*, Multiples of Median-Transformed, Normalized Reference Ranges of Steroid Profiling Data Independent of Age, Sex, and Units. *Horm Res Paediatr*, 1 (Apr 25, 2018).

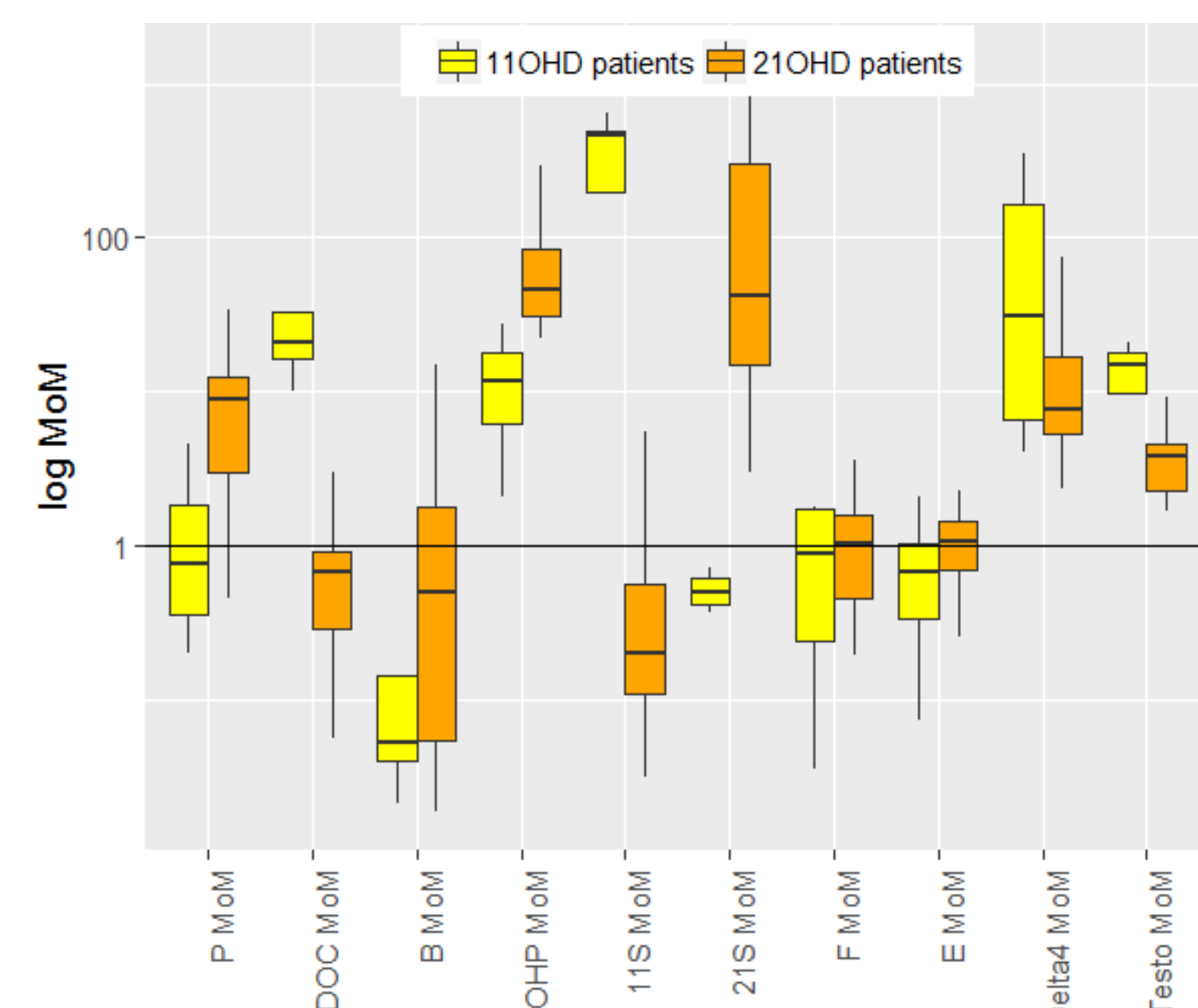


Fig. 5: MoM-transformed steroid profiles in 21OHD and 11OHD

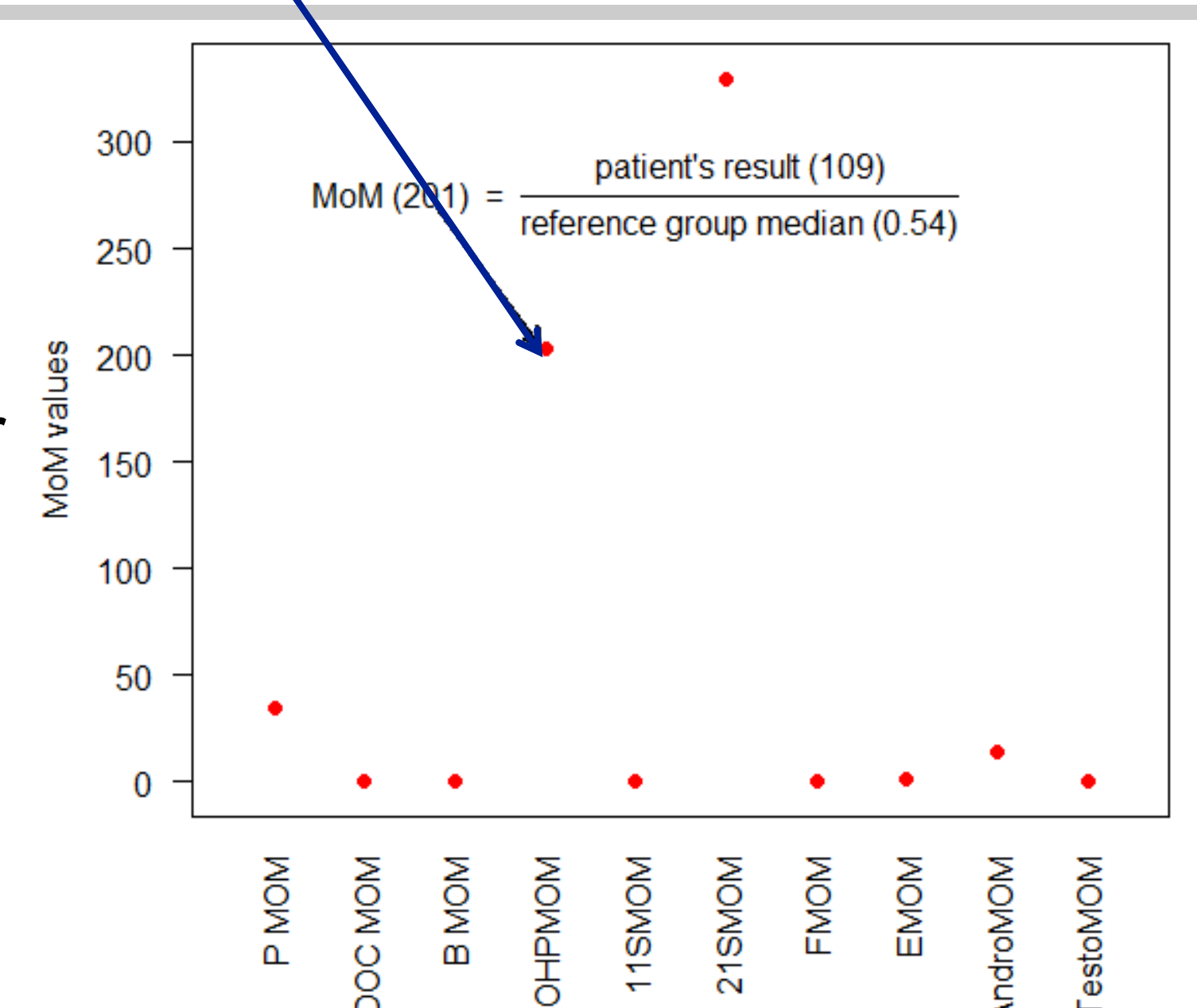


Fig. 4: MoM values of patient 2.

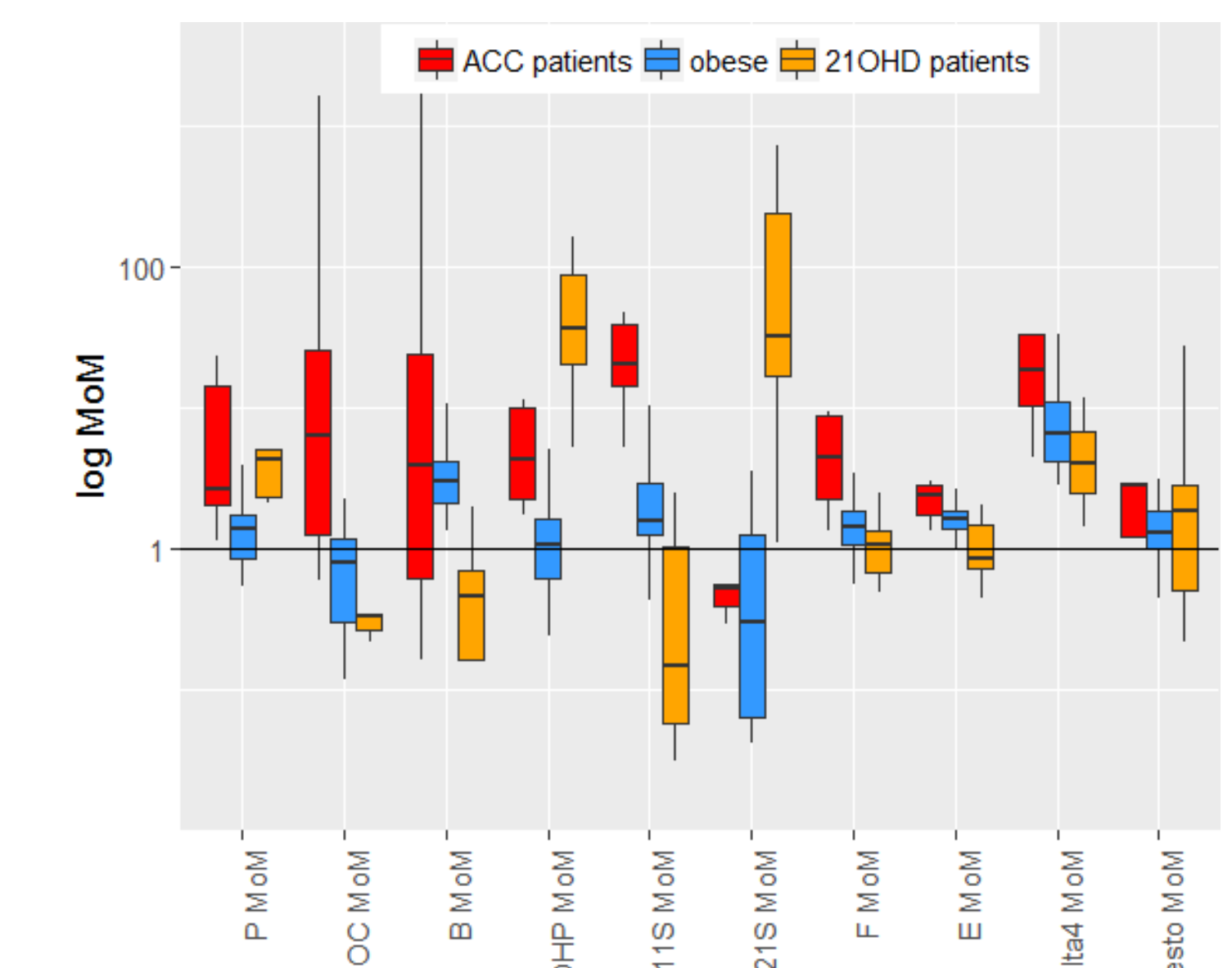


Fig. 6: Comparison of MoM patterns in ACC, obesity and 21OHD

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Adrenals and HPA axis:RFC1.6