

Supplementary Table 1: Summary of genetic and clinical data (n = 24)

ID	Age range (years)	Gender	DNMT3A variant NM_022552.5	Amino acid change	Protein domain (missense and <i>in frame</i> variants and intragenic deletion)	Variant class	Significance	Inheritance	Tall stature (height)	Macrocephaly (OF-C)	Weight ≥ 2SD	Overweight (BMI): IOTF>25	Advanced bone age	ID (level)	Craniofacial abnormalities
1	10-14	M	c.1634A>G	p.(Glu545Gly)	ADD	missense	likely pathogenic	<i>de novo</i>	No (+0.6 SD)	Yes	Yes (+3.3 SD)	Yes (+2.1 SD)	ND	Yes (mild-moderate)	Yes
2	10-14	M	c.1668G>C	p.(Arg556Ser)	ADD	missense	likely pathogenic	<i>de novo</i>	Yes (+2.3 SD)	No	No	No (-0.1 SD)	ND	Yes (moderate)	Yes
3	15-19	F	c.958C>T	p.(Arg320*) [†]	-	nonsense	pathogenic	<i>de novo</i>	Yes (+2.3 SD)	No (+1.5 SD)	Yes (+3.0 SD)	No (+1.1 SD)	Yes	Yes (moderate)	Yes
5	20-24	F	c.2525A>G	p.(Gln842Arg) [‡]	MTase	missense	likely pathogenic	<i>de novo</i>	No (+1.2 SD)	Yes (+2 SD)	Yes (+3.5 SD)	Yes (adult with BMI>25km/m ²)	Yes	Yes (severe)	Yes
6	20-24	F	c.1267G>T	p.(Glu423*)	-	nonsense	likely pathogenic	not maternal, absent in brother	Yes (+3.3 SD)	Yes	Yes (+4.6 SD)	No (adult with BMI<25km/m ²)	Yes	Yes (mild)	Yes
7	10-14	F	c.1903C>T	p.(Arg635Trp)	MTase	missense	likely pathogenic	inherited from affected mother	Yes (+2.4 SD)	Yes (+3.3 SD)	Yes (+2.9 SD)	No (+1.1 SD)	ND	Yes (mild-moderate)	Yes
8 (mother of patient 7)	35-39	F	c.1903C>T	p.(Arg635Trp)	MTase	missense	likely pathogenic	unknown	Yes (ND)	ND	ND	Yes (overweigh noticed by clinician)	ND	Yes (mild)	Yes
9	15-9	M	c.1430-1G>C	p.(?)	-	splicing	likely pathogenic	<i>de novo</i>	ND	ND	ND	ND	ND	Yes (moderate)	Yes
10	15-19	F	c.2311C>T	p.(Arg771*)	-	nonsense	pathogenic	<i>de novo</i>	No (+0.7 SD)	Yes (+4 SD)	Yes (+2.4 SD)	No (+1.2 SD)	Yes	Yes (moderate)	Yes
11	15-19	F	c.2711C>T	p.(Pro904Leu) [†]	MTase	missense	pathogenic	<i>de novo</i>	No (+0.5 SD)	Yes (+2 SD)	Yes (+4.2 SD)	Yes (+2.1 SD)	ND	Yes	Yes
12	10-14	M	c.2722T>A	p.(Tyr908Asn)	MTase	missense	pathogenic	<i>de novo</i>	Yes (+2.6 SD)	Yes	No	No (+0.8 SD)	ND	Yes, with regression	Yes
13	5-9	F	c.1078_1095dup	p.(Asn360_Tyr365dup)	Interaction DNMT1 and DNMT3B	<i>in frame</i> duplication	likely pathogenic	maternally inherited	Yes (+5.7 SD)	Yes (+2.8 SD)	Yes (+7.4 SD)	Yes (+2.0 SD)	ND	Developmental delay	Yes
14	10-14	F	c.1976G>A	p.(Arg659His)	MTase	missense	likely pathogenic	<i>de novo</i>	Yes (+4.3 SD)	Yes	Yes (+8.4 SD)	Yes (+2.6 SD)	ND	Yes (mild), developmental delay	Yes
15	15-19	M	c.2645G>A	p.(Arg882His) [†]	MTase	missense	pathogenic	<i>de novo</i>	No (+1.1 SD)	No (+1.5 SD)	No	No (+1.0 SD)	ND	Yes (severe)	Yes

16	10-14	M	c.745C>T	p.(Gln249*)	-	nonsense	pathogenic	<i>de novo</i>	Yes (+3.1 SD)	Yes (+2 SD)	Yes (+3.0 SD)	No (+1.1 SD)	ND	Yes, with regression	Yes
17	10-14	F	c.1904G>A	p.(Arg635Gln)	MTase	missense	pathogenic	<i>de novo</i>	Yes (+4.5 SD)	No (0 SD)	No	No (-1.2 SD)	Yes	Yes (mild-moderate)	Yes
18	10-14	M	c.427C>T	p.(Arg143*)	-	nonsense	pathogenic	<i>de novo</i>	Yes (+2.6 SD)	No (+0.5 SD)	Yes (+4.2 SD)	Yes (+2.0 SD)	ND	Yes, developmental delay	Yes
19	10-14	M	c.1925del	p.(Gly642Glnfs*9)	-	<i>frameshift</i>	likely pathogenic	unknown	No (ND)	No	ND	ND	ND	Yes, nonsyndromic	No
20	10-14	F	c.1684T>G	p.(Cys562Gly)	ADD	missense	pathogenic	<i>de novo</i>	No (+1.9 SD)	Yes (+3 SD)	Yes (+3.1 SD)	Yes (+2.0 SD)	ND	Yes (mild-moderate)	Yes
22	5-9	F	c.2711C>T	p.(Pro904Leu) [†]	MTase	missense	pathogenic	<i>de novo</i>	Yes (+3.3 SD)	Yes (+3.3 SD)	Yes (+2.3 SD)	No (+0.3 SD)	ND	Yes (mild)	Yes
23	10-14	M	c.1925G>T	p.(Gly642Val)	MTase	missense	likely pathogenic	<i>de novo</i>	Yes (+2.5 SD)	Yes (+3 SD)	Yes (+2.0 SD)	No (+0.5 SD)	ND	Yes, developmental delay	Yes
24	5-9	F	c.2644C>T	p.(Arg882Cys) [†]	MTase	missense	pathogenic	<i>de novo</i>	No (+1.7 SD)	No (+1.5 SD)	Yes (+4.9 SD)	Yes (+2.9 SD)	ND	Developmental delay	Yes
27	15-19	M		p.(Pro307Leu)	PWWP	missense	likely pathogenic	<i>de novo</i>	Yes (+3.2 SD)	Yes (+2.2 SD)	No	No (-0.8 SD)	ND	Yes	Yes
28	15-19	F	Del ex7-23	p.(?)	PWWP/ADD/MTase	intragenic deletion	pathogenic	<i>de novo</i>	Yes (+2.3 SD). marfanoid habitus	Yes (+2 SD)	Yes (+5.4 SD)	Yes (+2.2 SD)	ND	Yes	Yes

ND: no data

PWWP: proline-tryptophan-tryptophan-proline domain

ADD: ATRX-DNMT3-DNMT3L domain

MTase: Methyltransferase domain

[†] Variants previously reported

^ε Patient previously reported Ref.: Sweeney, K. J., Mottolese, C., Belot, A., Szathmari, A., Frappaz, D., Lesca, G., Putoux, A., & Di Rocco, F. (2019). The first case report of medulloblastoma associated with Tatton-Brown–Rahman syndrome. *American Journal of Medical Genetics, Part A*, 179(7), 1357–1361. <https://doi.org/10.1002/ajmg.a.61180>

Accepted manuscript