Research Square

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Neurodevelopmental Outcomes in Russell-Silver Syndrome and Variability by (Epi)genotype

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Abstract

Background:

Russell-Silver Syndrome (RSS) is a rare imprinting disorder associated with growth restriction, relative macrocephaly at birth, feeding difficulties in early age, protruding forehead and skeletal asymmetry. Primary molecular causes are loss of methylation within 11p15.5 imprinting control region (*H19/IGF2*), [11p15LOM] and maternal uniparental disomy of chromosome 7, [upd(7)mat]. There is limited research on neurodevelopmental outcomes in RSS patients.

Objective:

Determine prevalences of neurodevelopmental disorders in a large cohort of molecularly-confirmed RSS patients and compare these prevalences among the RSS diagnostic groups and US general population [genUS].

Methods:

297 subjects > 2 years old were divided by RSS molecular cause (including 11p15LOM n=164, upd (7) mat n=99). Questionnaires about neurodevelopmental disorder diagnoses and treatments were completed by guardian or adult self. Reported diagnoses were confirmed by a qualified specialist.

Results:

Speech articulation disorder prevalence was greater in upd(7)mat group (68%) than 11p15LOM group (24%), and both were significantly greater than in the US general population [genUS] (9%). Childhood speech apraxia was more prevalent in upd(7)mat group (24%) compared to 11p15LOM (3%) group, and both were greater than in genUS (0.1%). More upd(7)mat subjects had delayed onset of speech (>18mos) than 11p15LOM subjects (52% versus 20%).

Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) were more prevalent in upd(7)mat group (29% and 28%) than both the 11p15LOM group (16% and 5%) and the gen US (11.4% and 2.8%). The male to female distribution of ASD was ~1:1 in the upd(7)mat group, compared to 4.8:1 in the 11p15LOM group and 4:1 in genUS.

The prevalences of intellectual disability (IQ < 75) and learning disorders in the upd(7)group, were 22% and 39%, respectively, which were significantly higher than rates observed in 11p15LOM group (2% and 7%), and genUS (2.20% and 9%). However, while upd(7)mat group had a normal distribution in academic performance, 11p15LOM subjects were skewed with 69% performing in the top third of their classes.

Data showed a trend toward greater prevalence of movement disorders in the upd(7)mat group than observed in the 11p15LOM group.

Conclusions:

RSS due to upd(7)mat is associated with greater prevalence of several neurodevelopment disorders compared to 11p15LOM and genUS.

1. Background

Russell-Silver Syndrome (RSS) is a rare imprinting disorder primarily characterized by in-utero and post-natal growth restriction along with relative macrocephaly. Some studies report poorer neurodevelopmental outcomes associated with RSS, which are likely related to the particular molecular defects. Early intervention has been shown to significantly improve the long-term outcome for children with conditions such as autistic spectrum disorder, speech disorder, and learning disabilities. The objective of this study was to determine the prevalence of diagnosed neurodevelopmental disorders for two primary (epi)genotype RSS groups and analyze whether these prevalences differed between the groups and from the known general population. A better understanding of the risks would support pursuing (epi)genetic testing for children with suspicion of RSS and can encourage initiation of therapies even before clinical delays in development may be identified. An estimation of neurodevelopmental risk could also be helpful in prenatal genetic counselling.

An updated estimate of the prevalence of RSS is 1/15,866 live births (1) which is higher than previous estimates (1/30,000 to 1/100,000). The Netchine-Harbison clinical scoring system (NH-CSS) (2) was developed using prospective data and has 98% sensitivity with 89% negative predictive value. The six-factor criteria include 1) small for gestational age (SGA), 2) postnatal growth failure, 3) relative macrocephaly at birth, 4) protruding forehead, 5) body asymmetry, and 6) feeding difficulties. The RSS Consensus Statement (3, 4) recommends that testing for the known causes of RSS be considered if a patient scores at least four of these six NH-CSS criteria and that a diagnosis of RSS should now primarily be molecular (rather than clinical).

In previous cohorts 60% of patients with clinically diagnosed RSS were found to have an underlying molecular defect (3, 4): 5–10% of individuals had maternal uniparental disomy of chromosome 7 (hereafter referred to as upd(7)mat); approximately 50% had loss of methylation of the imprinting control region (H19/IGF2 or imprinting center 1 (IC1)) on chromosome 11p15 (hereafter referred to as 11p15LOM); rare cases have chromosome rearrangement involving IC1 or mutations in genes in the *IGF2* pathway (*HMGA2, PLAG1*, and *IGF2)* or *CDKN1C*.

Prior research has identified a broad range of neurodevelopmental issues in RSS patients. Motor delays are common to these children (5, 6, 7, 8) which may be related to the relative macrocephaly and low muscle mass. Speech delays in general have been noted for the combined group of RSS patients (6, 7, 9), while verbal dyspraxia (childhood apraxia of speech) has been specifically associated with upd(7)mat, possibly due to the involvement of the paternally-expressed *FOXP2* gene (10). Global developmental delays and/or learning disorders have been described in those with upd(7)mat RSS (2, 6, 7, 10, 11). In two strong studies, the upd(7)mat groups had lower cognitive profiles than the 11p15LOM (12, 13). Autism spectrum disorder has been reported more frequently in upd(7)mat patients (2, 12), and

yet executive function deficits were not reported higher in either 11p15LOM or upd(7)mat RSS patients (14). Finally, there have been a number of small studies associating the altered expression of the paternally expressed *SGCE* gene on chromosome 7q21 with a possible increased risk of myoclonus dystonia in patients with upd(7)mat RSS (15, 16, 17, 18).

This (epi)genotype-phenotype study describes the largest cohort to date of individuals with a confirmed molecular cause of RSS, focusing primarily on differences between the 11p15LOM and upd(7)mat groups. Data are included for some of the less common molecular causes of RSS in supplemental tables. This study final population had N = 284 molecularly confirmed RSS and N = 13 "alternative diagnoses" for a total N = 297[1]. Prevalences of neurodevelopmental diagnoses/performance including speech disorders, autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), intelligence, learning disabilities, academic performance, movement disorders, and mental health disorders were analyzed to look for (epi)genotype/phenotype differences.

[1]Updated RSS Consensus Statement (pending publication) restricts diagnosis of RSS to methylation changes at 11p15ICR1 and upd(7)mat, and places 11p15 IGF2 and CDKN1C variants into a separate (epi)genetic group.

2. Patients and Methods

2.1 Study Population:

The study population was recruited via email invitation from individuals/families who had communicated with The MAGIC Foundation's RSS/SGA Research & Education unit over the last 25 years. The majority of patients had participated in the annual MAGIC convention free clinic and/or were patients of study physician authors (SJ, MH, IN). Informed consent was obtained from all participants or their legal guardians. Subjects were excluded if age was less than 2 years, non-English speaking, history of severe neonatal intensive care unit (NICU) complications, incomplete questionnaire, or molecular testing/diagnosis results could not be confirmed. Of 407 patients sent a recruitment letter via email, 85.8% responded and 83.5% enrolled. Our final study population included N = 284 RSS (epi)genotypes, and N = 13 other (epi)genotypes with RSS features for a total of N = 297.[1](Fig. 1)

2.2 Questionnaire:

Subjects or their parents completed an online questionnaire about: 1) auxology at birth, 2 years, and final height, if available; 2) neurodevelopmental diagnoses including speech disorders, autism spectrum disorder, attention hyperactivity disorder (ADHD), intelligence; 3) school performance; 4) learning differences; 5) movement disorders; 6) mental health disorders; and 7) medical treatments, such as growth hormone therapy and suppression of early/precocious puberty. Respondents were asked whether a specialist diagnosed the subject with one of the diagnoses above, and if so, what type of provider, as well as questions on therapies and/or medications used for each diagnosis.

2.3 Anthropometric measurements:

For birth weight, length, and head circumference standard deviation scores (SDS), we utilized the Usher & McLean tables and adjusted for gestational age in weeks and days (19). At 24-months of age (+/-2 months), these same variables were calculated using NCHS NHANES data, and were corrected for age, but not gestational age, per convention (20). As more than 75% of the enrolled subjects were from the United States, the CDC/NCHS 0–36 month SD scores for weight, length and head circumference were used. For data analysis, the reported 24 month measurements were entered as lengths (measurement taken lying down), though some measurements may have been standing heights.

2.4 Molecular (epi)genetic results:

All participants submitted copies of molecular results performed at outside laboratories. After PHI/patient identity were removed, all results were reviewed by IN and confirmed as RSS (epi)genotypes or other (epi)genotypes. Study participants were classified into one of four general (epi)genotype groups 11p15LOM, upd(7)mat, other RSS (epi)genotypes[1] (11p15 maternal duplication or deletion, IGF2 and CDKN1C variants), and other (epi)genotypes presenting with RSS-like features (HMGA2 variant or deletion, PLAG1 variant, matUPD16 and matUPD20).

2.5 Statistical analysis:

Data are presented as means +/- standard deviation, median and range, or counts and percentages as indicated. Differences between group means were tested with T-test, or in the case of > 2 groups with ANOVA. Changes over time across groups were tested with mixed regression modeling to allow for missing data. Testing was Tukey's adjusted to correct for multiple testing. Differences in medians or ordinal ranked data were tested with Wilcoxon rank sum test. Categorical data were tested with Fisher's exact test. Sub-analysis of some developmental outcomes was restricted to cases at least 5 years of age and excluded any case with a family history of the given trait analyzed (ADHD, depression, anxiety, OCD, myoclonus-dystonia, tic disorder, and all intellectual and school-related questions). Multivariable logistic regression was used to assess differences in the rates of clinical outcomes across (epi)genetic groups while adjusting for potential confounders. Observed rates were compared to published National Prevalence rates with an Exact Binomial Test and Bonferroni corrected for multiple testing. All differences were considered significant at the two-sided p-value of < 0.05. Analysis was run with SAS v9.4 software.

3. Results

3.1 Molecular (epi)Genetic Groups:

Overall, 407 subjects were recruited, with 297 subjects with available data for analysis (Fig. 1). The "11p15LOM" group (n = 164) included n = 4 who were known at that time to have multi-locus imprinting disturbance (MLID). All four subjects had clinical features of 11p15LOM and the incidences of

neurodevelopmental conditions were similar to the 11p15LOM cohort (n = 160). For all analysis, these were treated as one group. The data for the specific MLID patients (n = 4) are shown in **Supplemental Table 1**.

The “upd(7)mat” group (n = 99) included subjects determined to have isodisomy (n = 22), complete heterodisomy (n = 2), and mixed heterodisomy (n = 37), with the others being undetermined. These subgroups were too small for intra-subgroup analyses.

The “other RSS (epi)genotypes” group (n = 21) consisted of 11p15 maternal duplication (n = 13), 11p15 paternal deletion (n = 3), 11p15 *IGF2* paternal variant (n = 4), and *CDKN1C* variant (n = 1).[1]

The “other (epi)genotypes with RSS features” group (n = 13) consisted of *HMGA2* deletion (N = 3), *PLAG1* mutation (n = 3), upd(16)mat (n = 2), and upd(20)mat (n = 5).

3.2 Demographics:

Detailed demographic information on all (epi)genetic diagnoses are listed in **Supplemental Table 1**. The average age in the 11p15LOM group was 11.5 years (median 9.1 years, range: 2.0–67.9) which was not different from the upd(7)mat group at 11.0 years (median 9.5 years, range: 2.0–34.9) ($p = 0.83$). The gender distribution also was not different between 11p15LOM and upd(7)mat (58% vs 52% male; $p = 0.31$). Median gestational age in the 11p15LOM group was 37.6 weeks (range: 30.0–42.0), compared to 37.0 weeks for the upd(7)mat group (range: 30.3–41.0; $p < 0.01$). Parental ages at conception were significantly higher in the upd(7)mat group than the 11p15LOM group. The median maternal age in the 11p15LOM group was 31.6 years (range: 17.4–42.1) versus 34.4 years (range: 19.6–46.2) in the upd(7)mat group ($p < 0.01$). Median paternal age in the 11p15 LOM group was 33.2 years (range 20.0 to 48.4) versus 35.7 years (range 26.4–58.0) in the upd(7)mat group ($p < 0.01$).

3.3 Growth:

Overall, 11p15LOM and upd(7)mat together had mean birth measurement SDS of -2.6 +/- 0.9 (wt) and −3.5+/-1.6 (lth). This combined RSS group also had notable head sparing, with a mean head circumference SDS [HC] of -0.9+/-1.2. These means are in line with the larger group of published data in the first RSS Consensus Statement (3).

In analyzing the growth data by (epi)genotype (Fig. 2), birth weight SDS was lower in the 11p15LOM group than the upd(7)mat group (-2.8+/-0.8 vs -2.2+/-0.8, $p < 0.01$), as was birth length SDS (-3.9+/-1.6 vs -2.8+/-1.5, $p < 0.01$), with length more restricted in-utero than weight in both groups. Being born SGA is a typical, but not universal, characteristic of RSS (3, 4), and in our study, 95.7% of 11p15LOM subjects, and 85.9% of upd(7)mat subjects, were born SGA in either weight and/or length. Despite the 11p15LOM group being statistically lighter and shorter at birth than the upd(7)mat group, birth HC was statistically similar (-0.8+/-1.2 and − 1.0+/-1.3 SDS, respectively; $p = 0.11$). Head sparing to length at birth, was therefore significantly larger in 11p15LOM vs upd(7)mat cohorts (3.2+/-1.8 vs 1.8+/-1.6 SD, $p < 0.01$).

Neither RSS cohort achieve linear catch-up growth into the normal range, but there was a difference in growth between the cohorts (Fig. 2). By 24-months, the length SDS of the 11p15LOM group improved to -2.8+/-1.2 SDS, while the length SDS of the upd(7)mat group decreased to -3.3+/-1.0 SDS (a significant difference, $p < 0.01$). And although both groups experienced a significant increase in their HC SDS between birth and 24-months, the 24-month HC was higher in the upd(7) group than the 11p15LOM group (0.6+/-0.9 SDS versus 0.1+/-1.0 SDS, $p < 0.01$). The change in HC and length over time results in a greater degree of head sparing at 24-months age for the upd(7) group compared to the 11p15LOM group (+ 3.8+/-1.1 vs. +2.8+/-1.3, respectively; $p < 0.01$). Direct statistical comparison cannot be made between newborn SDS derived from Usher and McLean and 24-months SDS from CDC.

3.4 Speech/Language/Communication:

Table 1 summarizes the prevalences of specific speech disorders by the two primary RSS (epi)genotype groups, among cases at least 2 years of age. Most speech and language disorders are more prevalent in RSS patients than the general U.S. population, and especially in the upd(7)mat group.

Table 1
Speech disorder prevalences among RSS subjects ≥ 2 years of age.

Speech articulation disorder	**11p15LOM**	**upd(7)mat**	**p-value[1]**	**Est. National Prevalence**
	24%* (37/154)	**68%* (61/90)**	**< 0.001**	**9%**
Speech apraxia (CAS)	2.5%* (4/159)	24%* (21/88)	**< 0.001**	0.1%
Social (pragmatic) communication disorder	1.2%[#] (2/163)	11% (10/94)	**< 0.001**	11%
Stutter	3.1% (5/160)	5.2% (5/97)	0.415	2%
Speech onset ≥ 18mo of age	20% (32/163)	52% (50/96)	**< 0.001**	
Currently nonverbal	1.2% (2/163)	6.1% (6/99)	**0.027**	

[1]Chi-square test, 11p15LOM to upd(7)mat.

*Significantly higher or [#]significantly lower than Estimated National Prevalence, Exact Binomial test.

3.5 Autism and Sensory Processing Disorder:

Among subjects who were at least 2 years old, our combined RSS population with ASD (n = 36) had 59% males and 41% females. ASD was significantly more prevalent in the upd(7)mat group than the 11p15LOM, and at a higher rate in both groups than the U.S. national (21) and/or worldwide prevalences (22) **(**Table 2**)**. The median age of diagnosis of ASD for upd(7)mat cohort was 5.4 years (range: 1.5–32.0), and 3.0 years (range:2.3–10.0) for the 11p15LOM cohort (p = 0.02).

Table 2
Autism Spectrum Disorder (ASD) prevalence among RSS subjects ≥ 2 years of age.

ASD diagnosis	**11p15LOM**	**upd(7)mat**	**p-value[1]**	**Est. National Prevalence**
	6.3%* (10/158)	**29%* (26/89)**	**< 0.001**	**2.8%**
ASD M:F	8:2	13:13*	0.142	4:1
ASD diagnosis, exclude fam hx	4.8% (7/145)	28%* (24/85)	**< 0.001**	
ASD M:F, exclude fam hx	6:1	12:12	0.191	

[1]Exact Fisher's test, 11p15LOM to upd(7)mat.

*Significantly higher than the Estimated National Prevalence, Exact Binomial test.

The prevalences of sensory processing disorder (SPD) and social (pragmatic) communication disorder (SCD) were higher in the upd(7)mat group (22% and 11%, respectively) than observed in the 11p15LOM group (4%, and1%; $p < 0.01$ for both). Significantly strong associations were found between a diagnosis of ASD and diagnoses of SPD, SCD and/or childhood apraxia of speech (CAS) $p < 0.01$ for each). Speech delay was also strongly associated with ASD diagnosis ($p < 0.01$). Given the overlap between the clinical features of these disorders and ASD, these strong correlations are consistent with the ASD diagnoses in this cohort.

3.6 Attention-Deficit/Hyperactivity Disorder (ADHD):

Excluding subjects younger than 5 years of age and those with a family history of ADHD, and after adjusting for sex differences, there was a greater prevalence of ADHD in the upd(7)mat group (29%, 19/66) compared to the 11p15LOM group (16%, 18/110; $p = 0.03$) and to the genUS group (11.4%; $p < 0.01$). The prevalence rates for 11p15LOM and genUS were not different. While there was a significant difference in the rate of ADHD by sex (all males: 27%; all females: 13%; $p = 0.04$) there was no significant difference in the sex distribution of ADHD by (epi)genotype ($p = 0.43$).

3.7 Intelligence/ Learning/ Academic Performance:

3.7.1 Intelligence

Intellectual disability (IQ ≤ 75) was more prevalent in the upd(7)mat group (21.5%, 14/65) than the 11p15LOM group (1.9%, 2/104; $p < 0.01$). None of the subjects with MLID (two MLID-11p15LOM & 14q3, one MLID-11p15LOM & ICR2) were reported to have an intellectual disability. Within cases with intellectual disability, there was no difference in the rate of ASD co-morbidity across (epi)genotype (11p15LOM: 2/2; upd(7)mat: 8/12; $p > 0.99$).

3.7.2 Learning Disabilities:

Diagnosis of one or more learning disabilities in cases 5 years of age or older was more prevalent in upd(7)mat group (39%, 29/75) than either the 11p15LOM group (7.0%, 9/129; $p < 0.01$) or the genUS (8.83%, $p < 0.01$). Reported learning disabilities that were more prevalent in upd(7)mat than 11p15LOM groups included dysgraphia (10% vs 2%; $p = 0.01$), language processing disorder (12% vs 0%, $p < 0.01$), non-verbal learning disability (9% vs 1%; $p = 0.01$), and auditory processing disorder (9% vs 1%; $p = 0.01$), respectively. There were no differences in rates of visual perceptual/visual motor deficit (6% vs 2%; $p = 0.11$), dyslexia 4% vs 3%; $p > 0.99$), or dyscalculia (5% vs 2%; $p = 0.20$)

3.7.3 Academic Performance:

For subjects 5 years of age or older who attended mainstream classrooms, the reported academic performance was significantly higher for the 11pLOM group than the upd(7)mat group. The upd(7)mat group was fairly evenly distributed across academic tertiles (see Fig. 3; **32**%/27%/41%), while the 11p15LOM group was skewed with higher rankings (69%/21%/9%; $p < 0.01$). Notably, while 11% of the upd(7)mat group ranked in the top 10th percentile, a significant 40% of the 11p15LOM group fell in this top decile ($p < 0.01$).

3.8 Movement Disorders:

For analysis, we excluded subjects younger than 5 years of age, and those with a family history of the same movement disorder as the subject (Table 3). Here we observed a significantly increased rate of having one or more diagnosed movement disorders in upd(7)mat versus 11p15LOM ($p = 0.01$), specifically notable with tic disorders ($p = 0.01$).

Table 3
Movement disorders among RSS subjects ≥ 5 years of age without any parental history

Diagnosed with one or more movement disorder	**11p15LOM**	**upd(7)mat**	**p value[1]**
	11%	**25%**	**0.011**
	(14 / 129)	**(19 / 77)**	
Epilepsy	3%	8%	0.178
	(4 / 129)	(6 / 76)	
Myoclonus dystonia[2]	1%	3%	0.292
	(1 / 129)	(2 / 72)	
Tic disorder	8%	20%	**0.014**
	(10 / 128)	(15 / 74)	
Non-febrile seizures	0%	4%	0.052
	(0 / 129)	(3 / 78)	
Tremors[2]	1%	4%	0.145
	(1 / 129)	(3 / 76)	
[1]Fisher Exact Test			
[2]Patients on ADHD simulant meds were excluded			

3.9 Mental Health Disorders:

For analysis, we excluded subjects younger than 5 years of age, and those with a family history of the same mental health disorder as the subject (Table 4). There was no significant difference between the two groups (small sample sizes impacting the analyses). However, the prevalences of anxiety and OCD were significantly higher in the upd(7)mat group compared to the estimated national prevalence (anxiety: 22% vs. 10.0%, p = 0.001; OCD: 8.8% vs. 4.0%, p = 0.042, respectively).

Table 4
Mental health disorders among RSS subjects ≥ 5 years of age without any parental history.

Anxiety	**11p15LOM**	**upd(7)mat**	**p value[1]**	**Estimated National Prevalence**
	10%	**22% ***	**0.063**	**9.4%**
	(11 / 109)	**(13 / 60)**		
Depression	6.6%	4.4%	0.749	4.0%
	(8 / 121)	(3 / 68)		
OCD	4.0%	8.8% *	0.198	4.0%
	(5 / 126)	(6 / 68)		

[1]Fisher Exact Test

*Prevalence values significantly higher than the Estimated National Prevalence, Exact Binomial Test; *p = 0.001* (anxiety) and *p = 0.042* (OCD)

4. Discussion

This study was designed to assess whether the prevalences of neurodevelopmental diagnoses differ between the two primary (epi)genotypes of Russell-Silver Syndrome (RSS), and to assess if upd(7)mat patients are at greater risk for several neurodevelopmental disorders compared to 11p15LOM patients as well as the U.S. general population.

Limitations to previous studies include small patient cohorts and/or case studies. As RSS is rare, it is difficult to evaluate a large group of patients at a single study location. Among the studies that have referenced neurodevelopmental issues in RSS (previously listed in the Background section), the molecularly confirmed cohorts ranged from one to 32 upd(7)mat and one to 47 11p15LOM subjects. Many of these studies included patients with clinical RSS or those who did not have confirmation of the molecular diagnosis, making it challenging to draw conclusions about differential risks in health, growth, and neurodevelopmental outcomes. Some studies included neurodevelopmental issues such as “speech delays” or “intellectual delays” without clear definitions.

The first RSS Consensus publication (3) included eight strong (epi)genotype-phenotype studies; however, the upd(7)mat data was relatively weak with a combined total of just 63 subjects (versus 201 subjects with 11p15LOM). Only four of these studies included limited data on neurocognitive or mental health issues (2, 6, 7, 9). Additional small phenotype-genotype studies and/or case studies were excluded because either their populations crossed over with one of the eight included studies or the clinically diagnosed populations lacked molecular testing. More recently, five studies have applied established neurodevelopmental testing methods to examine specific neurodevelopmental outcomes in small groups of RSS patients. Lane et. al. (2019) studied autistic traits and cognitive abilities with in-person

testing in n = 33 RSS patients (n = 79 completed SRS-2 questionnaire) (12). Patti et. al. (2020) examined cognitive profiles and brain volumes in n = 30 RSS patients (13). Burgevin et. al. published three studies using the same population of n = 19 11p15LOM, on quality of life/mental health, executive functioning, and intelligence function (14, 23, 24). Combined, these studies include just 47 upd(7)mat and 81 11p15LOM subjects.

Our study examined patient-reported neurodevelopmental diagnoses and analyzed prevalence data from a large group of RSS patients which allowed strong statistical power. We enrolled 83.5% of all RSS patients known to The MAGIC Foundation over the prior 25 years. This high enrollment rate diminishes the risk of enrollment bias, in which RSS patients with known neurodevelopmental issues may have been more likely to enroll in such a study. And the large number of RSS patients enrolled also provides strength to our prevalence data. However, participation in the MAGIC Foundation itself may be subject to selection bias, as families of less severely affected may be less likely to attend the annual convention. By excluding participants with NICU complications such as resuscitation or intracranial hemorrhage, we reduced the likelihood that an observed neurodevelopmental outcome was influenced by perinatal or early neurologic injury. Similarly, by excluding those with a positive family history of a particular neurodevelopmental disorder, we reduced the likelihood that the prevalence of the observed condition was influenced by inherited risk separate from RSS. These exclusions strengthen interpretation of our findings by minimizing potential confounding variables. Another strength of our study was the requirement for confirmation of each participant's molecular diagnosis. Upon our review of each subject's molecular results, we did identify a few subjects who initially reported an incorrect epigenetic diagnosis, highlighting the need to obtain confirmation of the underlying diagnosis before drawing conclusions.

The reported prevalence of upd(7)mat appears to be increasing over time. In 2024, Lin et al. identified n = 7 upd(7)mat (18%) compared to n = 31 11p15LOM (n = 82%) among patients scoring 4 + on the NH-CSS and receiving molecular testing for RSS (n = 183) (25). Previous articles described 10% prevalence of upd(7)mat (2, 3, 7), but included 30–40% of patients with clinically diagnosed RSS (with 45–55% with 11p15LOM, and 5% other CNVs/SNVs). In a cohort comprised only of 11p15LOM and upd(7)mat, the same number of upd(7)mat would therefore result in a prevalence of approximately 15–18%. In addition, advanced maternal childbearing age is associated with the development of UPDs (26). Both maternal and paternal ages at childbirth have been reported as significantly higher in upd(7)mat than 11p15LOM (6), and our study results echo this. Our cohort demonstrated higher parental ages in the upd(7)mat group versus 11p15LOM. In fact, we found an advanced maternal age at childbirth of ≥ 35 years in 46% of the upd(7)mat group and 21% of the 11p15LOM group, and an advanced paternal age at childbirth of ≥ 40 years in 25% of the upd(7)mat compared to 10% of the 11p15LOM. As parental age continues to rise in the general population (27, 28), this trend may have implications for a potential increase in the incidence of upd(7)mat.

Our study has an increased proportion of upd(7)mat patients for two other possible reasons. First and foremost, the MAGIC data covers more than 25 years of patient contacts, and 11p15LOM testing was

not readily available in the U.S. until around 2010. Prior to this, other than those molecularly diagnosed with upd(7)mat, patients were clinically diagnosed with RSS and many never went on to have molecular testing. As such, MAGIC's historical data of RSS molecularly confirmed patients is skewed towards a higher proportion of upd(7)mat patients than any particular group tested at a single point in time. Second, a slightly greater percentage of identified upd(7)mat patients (86%) enrolled in this study compared to 11p15LOM (80%).

Finally, although we did not directly assess each subject in-person using uniform neurodevelopmental diagnostic criteria, we did provide clear definitions for each neurodevelopmental diagnosis and ascertained the type of specialist who made the diagnosis.

Speech/Language/Communication:

RSS patients have been reported to have high rates of speech delays and/or disorders. The 2016 RSS Consensus (3) identified a 39.7% frequency rate of speech delays but most studies did not delineate the different forms of speech disorders or describe prevalence by (epi)genotype. Three previous studies of small RSS populations found higher rates of speech delays in upd(7)mat patients than other RSS (epi)genotypes (6, 7, 9). According to an U.S. NIH-related website (29), 8–9% of U.S. children aged 3–17 years-old experience speech sound disorders (such as articulation or phonological issues), while 3.3% have a language disorder.

Our study ascertained the prevalence of specific speech disorders among cases at least 2 years of age, comparing between the (epi)genotypes and with the general US population. Speech disorders, other than stuttering, were more prevalent in the upd(7)mat group than the 11p15LOM group. Speech articulation disorder and childhood apraxia of speech (CAS) were also more prevalent in both upd(7)mat and 11p15LOM than the general US population. More upd(7)mat subjects had delayed onset of speech (≥ 18 months) than 11p15LOM subjects but very few were reported to be non-verbal in either cohort. Of the subjects who reported the age of speech onset, the mean age was not different between the two groups. There was no difference across (epi)genotypes in the prevalence of stutter, which was similar to the general population.

A combination of factors likely contributes to speech delays often observed in RSS children. Many are born with low muscle tone (9), which can affect the oral-motor function. The common finding of a high, narrow palate (6) can affect proper tongue positioning as well as increase the risk of recurrent otitis media and conductive hearing loss, which can exacerbate speech articulation delays.

Childhood apraxia of speech (CAS), previously known as verbal dyspraxia, occurs when the brain does not communicate properly with the muscles used for speech, resulting in difficulty in accurately sequencing sounds into syllables or words and in combining words into sentences (30). The Forkhead-box P2 (*FOXP2*) gene on chromosome 7 was the first gene identified as being associated with speech and language disorders. Mutations in *FOXP2* have been shown to cause significant deficits in both language expression and comprehension (31, 32, 33, 34, 35). A 2017 article on *FOXP2*-related speech

and language disorders (30) noted that these disorders fall into two categories: "*FOXP2*-only-related speech and language disorder," caused by *FOXP2* gene disruption alone, and "*FOXP2*-plus speech and language disorders," which result from larger genetic anomalies such as copy number variants (e.g., gene deletions), structural variances (e.g., chromosome translocations or inversions), or upd(7)mat (30). *FOXP2*-plus disorders typically involve additional global developmental challenges (30).

The relationship between RSS upd(7)mat and FOXP2 gene function remains under investigation. Feuk et al. in 2006 studied 13 individuals with developmental verbal dyspraxia (DVD), dividing them into groups based on genetic characteristics (10). The RSS upd(7)mat group with DVD was found to be similar in speech disabilities to the group with a chromosome 7q31 deletion of the *FOXP2* gene on the paternal allele – both groups had severe speech delays and difficulties with speech output, and faced challenges with chewing, swallowing, and feeding during early childhood (10). The authors concluded that the absence of the paternal *FOXP2* gene (whether through a paternal deletion or a maternal UPD) likely contributed to this speech and language phenotype. In our study, almost 1 in 4 upd(7)mat subjects (24%) had CAS. Importantly, CAS requires specialized and intensive speech therapy techniques, and finding speech-language pathologists experienced in CAS will be essential for families.

Autism and Sensory Processing Disorder:

Autism spectrum disorder (ASD) is defined in the DSM-5-TR by persistent challenges in social communication and interaction, including difficulties with social reciprocity, nonverbal communication, and forming or maintaining relationships, while often exhibiting restricted, repetitive behaviors, interests, or activities. A diagnosis of ASD requires symptoms that cause significant impairment and may incorporate current and historical information, as symptoms can evolve with age or be masked by coping strategies (36). The prevalence of ASD has risen over time, though it is unclear if this reflects improved diagnostic testing or a growing incidence. The U.S. CDC estimates ASD affects 1 in 36 children (2.8% prevalence) (21), while the WHO reports a global prevalence of 1 in 100 children (22), with variability by country.

Previous studies with small sample sizes suggest that the risk of ASD is significantly higher in RSS upd(7)mat than that of the general population and the RSS 11p15LOM population (2, 12). Early work raised the possibility of a link between ASD and chromosome 7 disorders and/or upd(7)mat (10, 37). The 2015 Azzi et al. phenotype-genotype study (2) identified a significantly higher frequency of ASD in a small group of upd(7)mat patients (7/12, 58.3%) than those with 11p15LOM (2/35, 5.7%), clinical RSS with no molecular diagnosis (2/14, 14.3%), and SGA non-RSS (1/8, 12.5%). In 2020, Lane et al. investigated the relationship between 11p15LOM and upd(7)mat and ASD (12) with a subset of participants undergoing in-person assessments using the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2). The ADOS-2 results suggested a 33.3% rate of suspected ASD in the upd(7)mat group (n = 15), compared to 11.1% in the 11p15LOM group (n = 18).

Our study confirms the significantly increased risk of ASD in RSS upd(7)mat. Of patients two years and older, the upd(7)mat group had a higher prevalence of an ASD diagnosis (29%, 26/89) than either the

11p15LOM group (6.3%, 10/158) or the U.S. general population (2.8%). The prevalence of ASD in the 11p15LOM group was also higher than the genUS, although to a smaller degree. When we excluded patients with a parental and/or sibling history of ASD, the prevalence of the 11p15LOM group (4.8%) was no longer different from the genUS group while the increased risk remained in the upd(7)mat group.

While the Azzi et al. (2) and Lane et al. (12) studies did not control for a family history of autism, we show there was no difference in the rate of positive family history of ASD between the (epi)genotypes, strengthening our conclusion that upd(7)mat has a higher prevalence of ASD. Within the upd(7)mat cohort, no difference was observed in the rates of ASD across upd(7)mat heterodisomy sub-types, though notable for a small number of subjects. Future research would ideally examine regions of homozygosity on chromosome 7 in upd(7)mat patients to determine if specific sequences are associated with an ASD diagnosis.

The CDC reports ASD is approximately 3.8 times more prevalent in boys than girls (21, 38). Our data show that the male-to-female ratio in the 11p15LOM group was 4:1, similar to the U.S. general population, whereas the ratio in upd(7) group was close to 1:1. This even distribution of upd(7)mat ASD males and females supports the previous suspicion of a genetic link between chromosome 7 and ASD (10, 37). The rate of ASD in other RSS (epi)genotypes is unclear, due to the small size of the groups. The 11p15 maternal duplication group had 11 patients at least two years of age and 0.0% had been diagnosed with ASD, while the other (epi)genotype RSS groups each had only 1–4 patients, making a statistical analysis impossible.

Attention-Deficit/Hyperactivity Disorder (ADHD):

ADHD is a developmental disorder that emerges during childhood and is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that negatively impacts daily functioning and development (36). To meet diagnostic criteria, symptoms must appear before age 12 years, be evident in at least two settings (e.g., home, school, or work), and interfere with social, academic, or occupational functioning. The DSM-5-TR categorizes ADHD into three subtypes: predominantly inattentive (formerly known as ADD), predominantly hyperactive-impulsive, and combined (36). The prevalence of ADHD varies depending on criteria and demographics in each country. Using 2022 data, Danielson et al. estimated that approximately 1 in 9 (11.4%) U.S. children age 3–17 had ever been diagnosed with ADHD (39), with prevalence rates of 15% in boys and 8% in girls (38). Other studies estimate the prevalence ranges from 5% to 10%, influenced by factors such as state, age, and diagnostic methods (40, 41).

Although previous studies have highlighted attention and behavioral issues in children and adults with RSS (7, 11, 23, 24), recent research has provided clearer data on ADHD and executive function levels in RSS individuals. Burgevin et al. is the first study to look specifically at executive functioning in a group of RSS patients, with n = 16 11p15LOM and n = 3 upd(7)mat compared to a matched control group of non-RSS patients (14). Neither the RSS combined group nor the 11p15LOM group was statistically different in overall executive functioning from the matched control group, while the upd(7)mat group was too small to analyze separately (14). In our study, in patients 5 years and older without a family history of

ADHD, after adjusting for sex differences, the prevalence of ADHD was significantly greater in the upd(7)mat group (29%) than both the 11p15LOM group (16%) and the U.S. general population (11.4%).

Intelligence/ Learning/ Academic Performance:

Intelligence:

Most individuals with RSS are reported to have normal intelligence. Early published research on cognitive levels in RSS included patients with “clinical RSS” (11, 42), and studies have differed in how intelligence is measured, and how intellectual disability is defined. Three recent studies examined cognitive differences between upd(7)mat and 11p15LOM subjects. Patti et al. assessed IQ and brain volume in 30 Italian RSS patients, finding that the 11p15LOM group (n = 15, IQ 100.8) matched the AGA control group (n = 33) while the upd(7)mat group (n = 15, IQ 75.8) was significantly lower (13). Cognitive development in study RSS patients was unrelated to birth size, gestational age, gender, growth hormone therapy, or IGF-1/IGFB3 levels, and the severity of the Netchine-Harbison clinical score did not predict cognitive issues (13). Lane et al. utilized the General Conceptual Ability (GCA) rather than traditional IQ measurement and found the mean GCA level of the 11p15LOM group (N = 47, GCA 98.56) was similar to the control group while the upd(7)mat group (N = 32 GCA 79.86) was significantly lower (12). Lastly, Burgevin et al. noted that the full-scale IQ of the combined RSS group (FSIQ = 101.63) and the 11p15LOM group (FSIQ = 101.75) was similar to that of the control group (FSIQ107.89). The upd(7)mat group of just 3 subjects was too small to make comparisons (FSIQ = 101.00) (14). An earlier study of Burgevin et al. on a small group of 11p15LOM adults (n = 10) found a mean FSIQ score of 95.4 which did not differ statistically from normative data (23).

In our study, the upd(7)mat group reported a significantly higher prevalence of intellectual disability than the 11p15LOM group (21.5% vs. 1.9%). These results are in line with those of Patti et al. (12), in which IQ was measured. The rate of intellectual disability appears to be higher in upd(7)mat, regardless of a concurrent diagnosis of ASD. Although the questionnaire defined intellectual disability as IQ ≤ 75, we did not request verification of formal IQ testing.

Learning Disabilities:

The overall prevalence of learning disabilities among U.S. children aged 6–17 years from 1997 to 2021 was identified as 8.83% (43). According to the CDC, between 2004 and 2006, 5% of children without low birth weight and 8% of children with low birth weight were diagnosed with learning disabilities, excluding ADHD (44). Previous RSS studies indicated a greater need for educational support services for upd(7)mat children than for those with 11p15LOM. For example, Wakeling et al. found that 9% of RSS 11p15LOM patients received educational support services compared to 25% of RSS upd(7)mat patients (7). And Azzi et al. reported that 75% of upd(7)mat patients required academic support services compared to only 17.4% of children with 11p15LOM (2). But neither study provided details as to what defined “educational” or “academic” support services. Educational support services may be provided for any number of reasons and may not be an accurate reflection of a diagnosed learning disability. More

recently, in Patti et al., the RSS upd(7)mat group showed deficits in verbal comprehension, perceptional reasoning, and working memory (13) which were not present in 11p15LOM patients. In contrast, Lane et al. observed no significant differences between RSS (epi)genotypes in cognitive subgroups including verbal ability, non-verbal reasoning, and spatial ability (12).

In our combined RSS group (11p15LOM and upd(7)mat) ≥ 5 years old, 18.6% reported at least one learning disability. However, when analyzed by (epi)genotype, the upd(7)mat study group reported a significantly higher prevalence of learning disabilities (38.7%) compared to the 11p15LOM group (7.0%) and compared to the general population (8.83%); the latter two were similar to each other. While dyslexia and dyscalculia rates were similar between the two RSS groups, other learning disorders such as language processing, dysgraphia, non-verbal learning, and auditory processing disorders were more prevalent in upd(7)mat RSS patients than 11p15LOM. This analysis highlights the importance of understanding the phenotypic differences between RSS (epi)genotypes.

Academic Performance:

In our questionnaire, participants were asked to compare the subject's academic standing with same-age classmates over the past two years, categorizing performance into top, middle, or bottom third. The upd(7)mat group was similar to the general population, fairly evenly distributed across academic tertiles despite the higher prevalence of learning disabilities. In contrast, the 11p15LOM group was significantly different from the upd(7)mat group with 69% in the top third of their class, 21% in the middle and 9% in the bottom third. Notably, 40% of the 11p15LOM group ranked in the top 10th percentile, significantly higher than the 11% of the upd(7)mat group. Patti et al's. study described reduced brain volume of gray matter of the frontal and temporal lobes and globi pallidi in RSS patients compared to the control group (13). The authors speculated whether there may be a potential link between IGF-1 expression and IGF-1 receptors in areas of the brain and cognitive differences in RSS 11p15LOM and upd(7)mat groups.

Two recent studies on RSS adults in the U.K. and France demonstrate that despite reporting learning difficulties and/or receiving special education support (27% and 60%, respectively), 40% of U.K. adults completed university degrees and 70% of French adults pursued higher education (8, 23). Our results highlight the diversity of academic achievement among individuals with RSS, mirroring that of the general population, regardless of the presence of learning disabilities or other neurodevelopmental diagnoses.

Movement Disorders:

Case reports linking RSS upd(7)mat and movement disorders were initially published in 2008–2010 (45, 46, 47). In 2010, Wakeling et al. reported that 15% of upd(7)mat individuals exhibited movement disorder symptoms (one each with tics, tremors, and myoclonic jerks), compared to none in the 11p15LOM group (7). Since that time, a number of other case studies on RSS upd(7)mat individuals diagnosed with movement disorders and/or myoclonus-dystonia have been published (15, 16, 17, 18, 48). Myoclonus-dystonia (M-D) is characterized by bilateral involuntary muscle jerks or twitches, accompanied by

involuntary tensing of specific muscles (16, 49). The maternally imprinted SGCE gene, located on chromosome 7q21.3, has been implicated as one cause of M-D. Clinical manifestations may arise when the expression of the paternal SGCE gene is altered due to gene mutation, deletion, or upd(7)mat (50, 51, 52). However, not all cases of M-D involve SGCE gene abnormalities, and not all upd(7)mat patients develop M-D.

This study assessed the prevalence of movement disorders including tics, tremor, epilepsy/seizure, and M-D in subjects at least 5 years old, without family history of that disorder. The small number of subjects in each group limited individual disorder analysis. However, the upd(7)mat group had a greater trend toward having at least one movement disorder compared to the 11p15LOM group (25% vs. 11%). Previous studies described that a significant proportion of patients with ASD (with or without RSS) are also diagnosed with seizures and/or epilepsy (53, 54). Of our RSS patients diagnosed with epilepsy, 71.4% (5 of 7) of upd(7)mat and 20% (1 of 5) of 11p15LOM were also diagnosed with or being investigated for ASD.

Until clearer knowledge is gained through future research, upd(7)mat patients should be monitored with particular attention to tics, tic disorders, tremors, and seizure activity, including epilepsy. Simple tics are common and transient in young children. A 2020 case report raised the question of whether myoclonus-dystonia is underreported in matUPD7 patients (48). The report described a 14-year-old girl with RSS upd(7)mat who had experienced hand jerks since age 6 years. Initially diagnosed with tremors and epilepsy, she was treated pharmacologically, and was subsequently diagnosed with myoclonus-dystonia (48). Children with upd(7)mat who have movement disorders should have careful monitoring with a pediatric neurologist with consideration of M-D in the differential diagnosis.

Mental Health Disorders:

The prevalence rates of mental health disorders can vary significantly based on variable, including but not limited to age, country, gender, era, and geopolitical events. Anxiety and depression are well-documented to occur at significantly higher rates in individuals with chronic illnesses (55, 56, 57, 58, 59, 60, 61). Previous studies of RSS adults reported appearance-related concerns, including dysmorphism, thinness, asymmetry, and short stature, but did not provide specific data on mental health diagnoses (8, 22, 62). Lokulo-Sodipe et al. found that quality-of-life scores of RSS adults were not significantly different from those of the general U.K. population (8). Burgevin et al., in a series of psychometric assessments, found that a small group of adults with RSS (n = 19) did not exhibit higher levels of anxiety or lower self-esteem compared to a control group without RSS (24). However, while the mean total self-esteem score for RSS adults was comparable to that of the controls, 45% of RSS participants had very low self-esteem (24).

In our analysis, although the prevalences of anxiety, depression, and obsessive compulsive disorder (OCD) were not significantly different between the two RSS cohorts, the upd(7)mat group had a significantly higher prevalence of anxiety and OCD compared to the general US population. Some research has linked individuals with myoclonus-dystonia and/or SGCE gene anomalies to a significantly

increased risk of psychiatric conditions, including phobias, anxiety disorders, and obsessive-compulsive disorder (50, 51, 52) though causative relationship has not been identified.

5. Conclusion

Neurodevelopmental disorders involve a complex interplay of genetic/epigenetic and environmental factors, making it difficult to predict outcomes for an individual. Our study shows that specific (epi)genotypes in RSS are linked to differing risks for certain neurodevelopmental conditions, with upd(7)mat individuals having a significantly higher risk overall. This may be due to additional imprinted genes on chromosome 7 compared to 11p15, and/or the potential presence of genes anomalies duplicated by the disomy, in favor of recessive expression. Our findings support the need to move beyond reporting outcomes for the combined RSS group. Early molecular testing in children with suspicion for RSS can provide valuable information to guide timely developmental screening and interventions. A multidisciplinary care team might include a developmental behavioral pediatrician, speech and language pathologist, pediatric neurologist, educational therapist, and mental health specialist.

These results may also help guide prenatal counselling. However, a diagnosis of upd(7)mat or 11p15LOM RSS cannot predict a consistent clinical outcome because of the wide range in phenotype. The majority of individuals with RSS in our study were able to engage in mainstream education, and many excel with above-average performance. Although patients with upd(7)mat had a higher prevalence of intellectual disability, more than 75% were within normal ranges. Similarly, although upd(7)mat patients had a 4-fold increase risk of ASD, 59% were in the middle or upper tercile of their class.

Further mapping of chromosome 7 may help identify imprinted and/or recessive genes that contribute to autism susceptibility and/or other neurodevelopmental disorders. Finally, gathering more genotype-phenotype data will help identify any differences between patients with complete isodisomy or heterodisomy upd(7)mat.

Abbreviations

RSS	Russell-Silver Syndrome
SGA	Small for Gestational Age
AGA	Appropriate for Gestational Age
IUGR	Intrauterine Growth Retardation
NICU	Neonatal Intensive Care Unit
11p15LOM	11p15 loss of methylation
upd(7)mat	Maternal uniparental disomy of chromosome 7
MLID	Multi-Locus Imprinting Disturbance
genUS	US general population
SDS	Standard Deviation Score
ADHD	Attention-Deficit/Hyperactivity Disorder
ASD	Autism Spectrum Disorder
SPD	Sensory Processing Disorder
SCD	Social communication disorder
CAS	Childhood Apraxia of Speech
DVD	Developmental Verbal dyspraxia
IQ	Intelligence Quotient
M-D	Myoclonus-Dystonia
OCD	Obsessive Compulsive Disorder

Declarations

Ethic approval and consent to participate:

Study application to Cedars-Sinai Institutional Review Board was granted approval by the chairman of Departmental Scientific Merit Review, through expedited non-committee review

• Cedars-Sinai, Office of Research Compliance and Quality Improvement, STUDY00000843

• Subjects or guardians signed consent form approved by IRB

• Research was conducted in accordance with the Declaration of Helsinki

Consent for publication: Not applicable

Availability of data and materials:

- All data analyzed during this study are included in this published article [and its supplementary information files]. Additional datasets are available from the corresponding author on reasonable request.

Competing interests:

- The authors declare that they have no competing interests

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Authors' contributions:

- SJ designed study/questionnaire, submitted IRB, wrote manuscript
- TGS assisted in study/questionnaire design, performed all RedCap coding for questionnaire and data management; was a substantial contributor in writing the manuscript.
- JS assisted with study/questionnaire design, IRB submission, study communications subject recruitment & enrollment, and was a major contributor in writing the manuscript.
- CB performed all statistical analysis, created figures and tables.
- IN reviewed all molecular results for RSS (epi)genotypes or other (epi)genotype and revised the manuscript
- YG and MDH revised the manuscript

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Figures

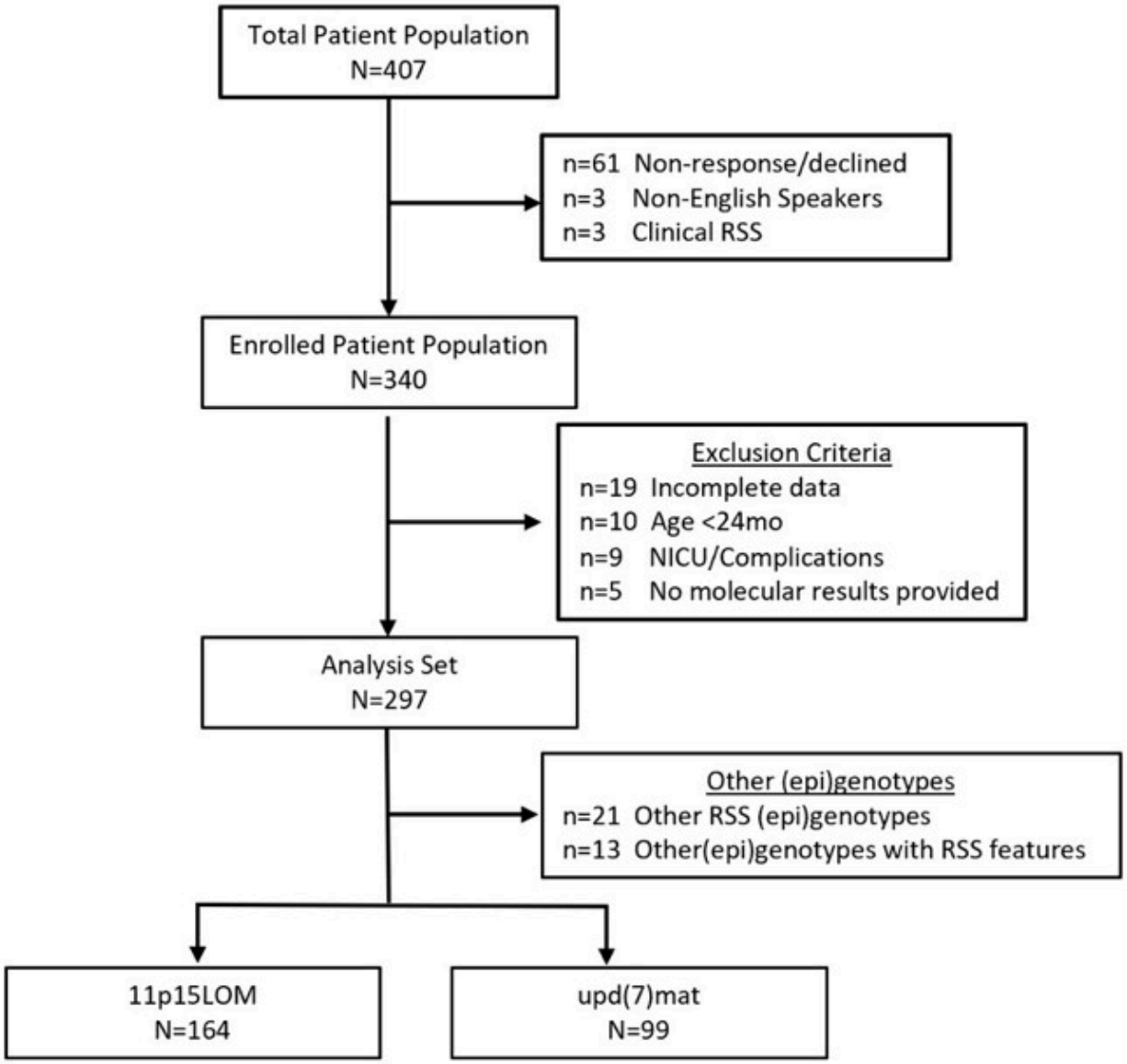

Figure 1

CONSORT diagram of patient enrollment.

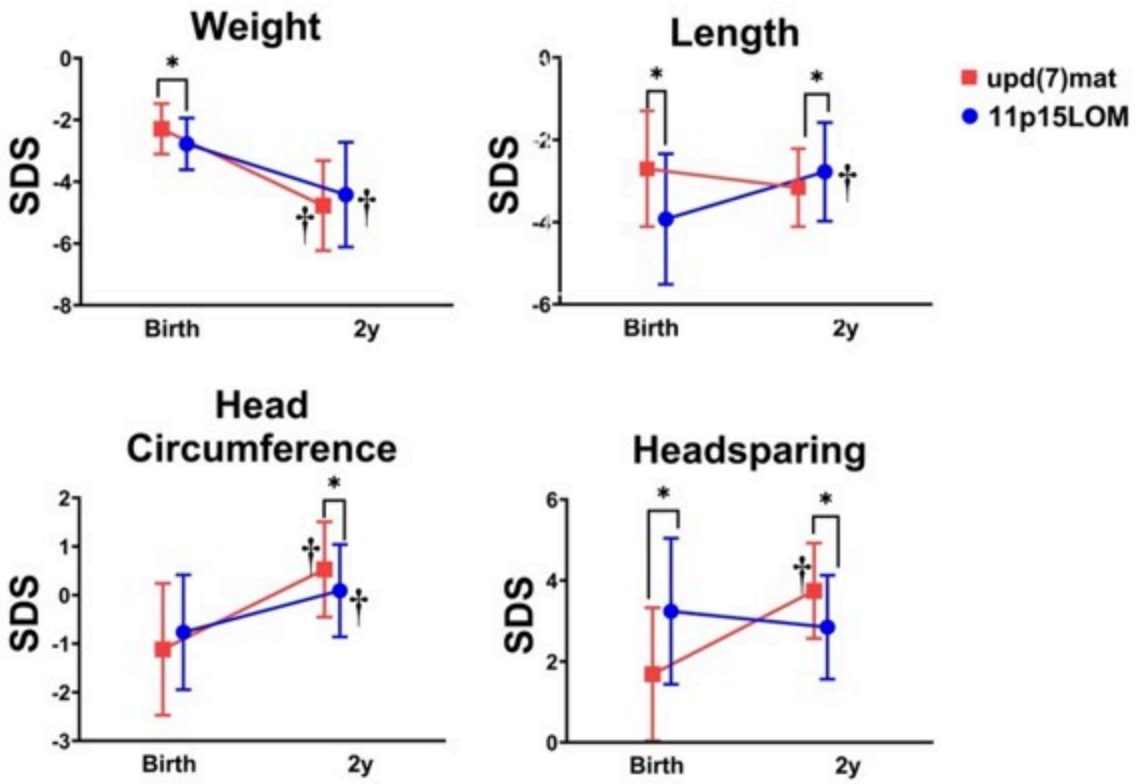

Figure 2

Standard deviation scores (SDS) for study subjects at birth and at 24 months of age by RSS (epi)genotype [2]

*Significantly different by genotype within age.

†Significantly different change over time within each genotype.

2 Test Methods: equal variance T-test for length & weight difference; Wilcox test for HC difference; chi-square test for head sparing

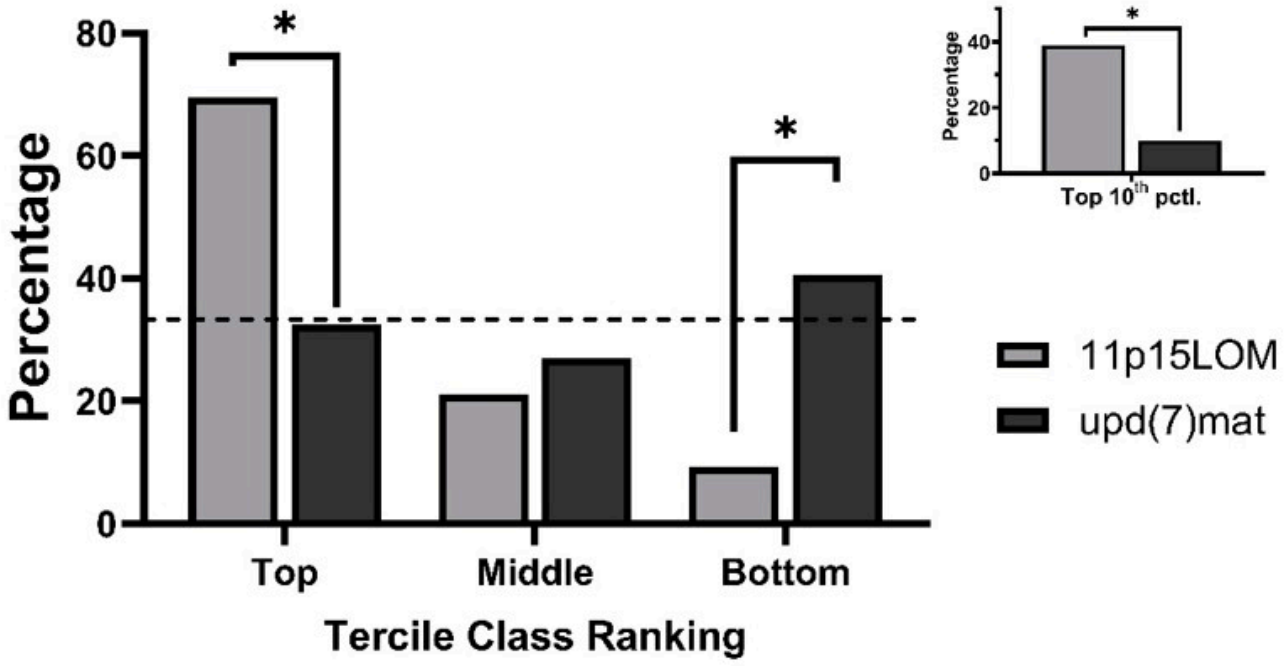

Figure 3

Academic performance compared to their classmates among RSS subjects ≥ 5 years of age.

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