

**Supplementary Table 1. Therapy Outcome Measures Scores and Additional Classification used in this study.**

<b>TOMs Categories</b>	<b>Classification</b>
<b>0</b> No autonomy, isolated, no social/family role <b>1</b> Very limited choices, contact mainly with professionals, no social or family role, little control over life	<b>Severe</b> communicative participation difficulty
<b>2</b> Some integration and autonomy in one setting <b>3</b> Integrated, valued and autonomous in limited number of settings	<b>Moderate</b> communicative participation difficulty
<b>4</b> Occasionally some restriction in autonomy/integration or role <b>5</b> Integrated, valued, occupies appropriate role	<b>Appropriate/Mild</b> communicative participation difficulty

**Supplementary Table 2. Speech and resonance in AS according to genotype.**

	<b>Cleft Palate n (%)</b>	<b>Speech Sound Disorder n (%)</b>	<b>Cleft-type speech characteristics n (%)</b>	<b>Hyponasal resonance n (%)</b>	<b>Hypernasal resonance n (%)</b>	<b>Mixed resonance n (%)</b>
<i>S252W</i>	18 (64%)	27 (96%)	2 (27%)	11 (73%)	3 (20%)*	1 (0.6%)**
<b>Total</b>	<b>28</b>	<b>28</b>	<b>27</b>	<b>15</b>	<b>15</b>	<b>15</b>
<i>P253R</i>	8 (35%)	21 (100%)	-	9 (75%)	2 (17%)	1 (0.8%)
<b>Total</b>	<b>23</b>	<b>21</b>	<b>0</b>	<b>12</b>	<b>12</b>	<b>12</b>

\*2/3 had cleft palate

\*\* Patient had submucous cleft palate

**Supplementary Table 3.** Language Development in AS according to genotype.

	Receptive Language difficulties n (%)				Expressive language difficulties n (%)			
<i>S252W</i>	21 (88%)				22 (88%)			
<b>Total</b>	24				25			
<b>Severity</b>	<b>No Data Available</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>	<b>No Data Available</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
	1	-	2	18	2	1	2	20
	Receptive Language difficulties n (%)				Expressive language difficulties n (%)			
<i>P253R</i>	17 (85%)				16 (80%)			
<b>Total</b>	20				20			
<b>Severity</b>	<b>No Data Available</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>	<b>No Data Available</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>
	6	1	2	10 (1)*	7	1	1	10 (1)*

\*One patient had severe difficulties that resolved with intervention.

**Supplementary Table 4.** Type of loss, severity and management of hearing loss in AS according to genotype.

	Nature of Hearing Loss		Severity of Hearing Loss		Tympanometry				OME	Affected frequencies		Management of Hearing Loss		
	Conductive n, %	Mixed n, %	Mild Loss n, %	Moderate Loss n, %	Type B bilaterally n, %	Type A bilaterally n, %	Unilateral right Type B n, %	Unilateral left Type C n, %		Low frequency sloping HL n, %	Flat hearing across all frequencies n, %	Grommets n, %	Hearing aids n, %	Hearing Aids and Grommets n, %
S25 2W	15 (94%)	1 (6%)	11 (52%)	10 (48%)	10 (59%)	5 (29%)	1 (0.3%)	1 (0.3%)	20 (100%)	16 (94%)	1 (6%)	3 (23%)	5 (38%)	5 (38%)
Total	16	16	21	21	17	17	31	31	20	17	17	13	13	13
P25 3R	14 (100%)	-	10 (66%)	5 (33%)	15 (59%)	2 (12%)	-	-	17 (89%)	13 (93%)	1 (0.7%)	8 (57%)	4 (29%)	4 (14%)
Total	14	-	15	15	17	17	-	-	19	14	14	14	14	14

**Supplementary Table 5.** *Communicative Participation as measured on the categories assigned to the TOMs according to genotype*

	<b>Mild*</b>	<b>Moderate</b>	<b>Severe</b>	<b>Total</b>
<i>S252W</i>	6	9	16	31
<i>P253R</i>	12	4	2	18
<b>Total</b>	<b>18</b>	<b>13</b>	<b>18</b>	<b>49</b>
<i>(p=0. 0005) Cochran Armitage</i>				

*\*No patient had appropriate communicative participation*

**Supplementary Table 6.** Additional neurodiverse diagnoses in AS according to genotype.

	Attention and Concentration Difficulties n, %	Autism Spectrum Disorder (ASD) n, %	Referred for Further Assessment of Possible ASD n, %	Social Communication Difficulties n, %
<i>S252W</i>	18 (95%)	4 (13%)	2 (6%)	11 (35%)
<b>Total</b>	<b>19</b>	<b>31</b>	<b>31</b>	<b>31</b>
<i>P253R</i>	14 (88%)	1 (4%)	1 (4%)	9 (39%)
<b>Total</b>	<b>16</b>	<b>23</b>	<b>23</b>	<b>23</b>

**Supplementary Table 7. Schooling and speech and language therapy support according to genotype**

	Mainstream School	Special School	Access to Speech and Language Therapy
<i>S252W</i>	10 (45%)	12 (55%)*	25 (81%)
<b>Total</b>	<b>22</b>	<b>22</b>	<b>31</b>
<i>P253R</i>	15 (70%) ^	7 (33%)**	83% (n=19/23) ***
<b>Total</b>	<b>21</b>	<b>21</b>	<b>23</b>

\* Two of whom started in mainstream primary school and transitioned to special school for secondary education

\*\* One of whom started in mainstream primary school and transitioned to special school for secondary education

\*\*\* One patient's support was for feeding and not communication development.

^ One patient started in special education, then returned to mainstream school.

**Supplementary Table 8.** Genetic, Speech, Language and Hearing Characteristics of Patients with AS

Patient Number	Gender	Nucleotide Substitution	Amino Acid Substitution	Laterality of Hearing Loss	Type of Hearing Loss	Severity of Hearing Loss	Tympanometry	Otitis Media with Effusion	Cleft	Receptive Language Difficulties	Receptive Severity	Expressive Language Difficulties	Expressive Severity	Speech Sound Disorder	Resonance	ASD	Schooling	Communicative Participation Classification
1	M	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	Yes	Yes	Severe	Yes	Severe	Yes	Hyponasal	Yes	Special School	Severe
2	M	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Moderate	Bilateral Type A	Yes	Yes	Yes	Severe	Yes	Severe	Yes	No	?ASD/Waiting Ax	Special School	Severe
3	M	c.755C>G	p.(Ser252Trp)	Bilateral	-	Moderate	Bilateral Type B	Yes	-	No	Appropriate skills	Yes	Severe	Yes	Hyponasal	?ASD/Waiting Ax	Mainstream School	Mild
4	F	c.755C>G	p.(Ser252Trp)	Bilateral	-	Mild	Bilateral Type B	Yes	-	Yes	Moderate	Yes	Mild	Yes		Yes	-	-
5	M	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Moderate	Bilateral Type B	Yes	Yes	Yes	Severe	Yes	Severe	Yes	Hyponasal	Yes	Mainstream School	Severe
6	M	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Moderate	Bilateral Type B	Yes	No	Yes	Severe	Yes	Severe	Yes (secondary to brain injury and occlusal difficulties)	Hyponasal	Yes	Special School	Severe
7	F	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	-	Yes	Severe	Yes	Severe	Yes	Hyponasal	Yes	Special School	Severe
8	F	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	No	Yes	Severe	Yes	Severe	Yes	Hyponasal	No	Special School	Severe
9	F	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	No	Yes	Severe	Yes	Severe	Yes	Hyponasal	Yes	-	-
10	F	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Moderate	Bilateral Type A	No	Yes	-	-	-	-	Yes (Cleft speech characteristics and due to occlusal difficulties)	Hypernasal	Yes	-	Moderate
11	F	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	No	-	-	-	-	Yes	Hypernasal	Yes	Mainstream School	Mild
12	M	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Mild	Right Type B, Left Type C	Yes	Yes	-	-	-	-	Yes	Hyponasal	Yes	-	Severe
13	M	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Moderate	Bilateral Type B, Poss Perf Left	Yes	Yes	-	-	-	-	Yes	Hypernasal	Yes	-	Mild
14	M	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	No	-	-	-	-	Yes	Hyponasal	Yes	Mainstream School	Moderate
15	F	c.755C>G	p.(Ser252Trp)	Unilateral	Conductive	Mild	Bilateral Type B	Yes	No	Yes	Severe	Yes	Severe	Yes	Hyponasal	Yes	Mainstream School>Special School	Severe
16	M	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	Yes	Yes	Severe	Yes	Severe	Yes	Hyponasal	Yes	Special School	Severe
17	F	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Moderate	Bilateral Type B	Yes	Yes	Yes	Severe	Yes	Severe	Yes	Hyponasal	Yes	Special School	Moderate
18	M	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	Yes	Yes	Severe	Yes	Severe	Yes	Hyponasal	Yes	Special School	Severe



19	F	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Moderate	Bilateral Type B	Yes	Yes	Yes	Severe	Yes	Severe	Yes	Hyponasal	No	Mainstream School	Severe
20	M	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	No	Yes	Severe	Yes	Severe	Yes	Hyponasal	Yes	Special School	Severe
21	F	c.755C>G	p.(Ser252Trp)	Unilateral	Conductive	Mild	Bilateral Type B	Yes	Yes	Yes	Moderate	Yes	Moderate	Yes	Hyponasal	Yes	Mainstream School	Severe
22	F	c.755C>G	p.(Ser252Trp)	Bilateral	5	Moderate	Bilateral Type B	Yes	No	Yes	Severe	Yes	Severe	Yes	Hyponasal	No	Mainstream School	Mild
23	M	c.755C>G	p.(Ser252Trp)	Unilateral	Conductive	Mild	Bilateral Type A	No	No	Yes	Severe	Yes	Severe	Yes	Hyponasal	Yes	Special School	Moderate
24	F	c.755C>G	p.(Ser252Trp)	Appropriate	N/1	-	Bilateral Type B	Yes	Bifid Uvula	No	Appropriate skills	No	Appropriate Skills	No	No	No	-	-
25	M	c.755C>G	p.(Ser252Trp)	4	-	4	Bilateral Type A	No	Yes	Yes	Severe	Yes	Severe	Yes	No	No	0	-
26	F	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	Yes	Yes	Appropriate skills	Yes	Severe	Yes	Mixed	Yes	-	Moderate
27	F	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Moderate	Bilateral Type B	Yes	Yes	Yes	Severe	Yes	Severe	Yes cleft speech characteristics	Hyponasal	No	Mainstream School	-
28	F	c.755C>G	p.(Ser252Trp)	Appropriate	N/A	-	Bilateral Type A	No	No	Yes	Severe	Yes	Severe	Yes	Hyponasal	?ASD/Waiting Ax	Special School	Severe
29	M	c.755C>G	p.(Ser252Trp)	Bilateral	-	Mild	Bilateral Type B	Yes	Bifid Uvula	No	Appropriate skills	No	Appropriate Skills	Yes	Hyponasal	No	Mainstream School	Mild
30	F	c.755C>G	p.(Ser252Trp)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	Yes	No	Appropriate skills	No	Appropriate Skills	Yes	Hyponasal	Yes	Mainstream School	Moderate
31	F	c.755C>G	p.(Ser262Trp)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	Bifid Uvula	-	-	-	-	No	Hyponasal	No	Mainstream School >Special School	Moderate
32	F	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	No	Yes	Severe	Yes	Severe	Yes	Hyponasal	No	Special School	Mild
33	M	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Moderate	Bilateral Type B	Yes	No	No	Appropriate skills	No	Appropriate Skills	Yes	Hyponasal	No	Mainstream School	Mild
34	F	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Moderate	Bilateral Type B	Yes	Bifid Uvula	Yes	Mild	Yes	Mild	Yes	Hyponasal	No	Mainstream School	Mild
35	M	c.758C>G	p.(Pro253Arg)	Appropriate	N/A	-	Bilateral Type A	No	No	Yes	Severe	Yes	Severe	Yes	Hyponasal	No	Special School>Mainstream School	Moderate
36	F	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	No	No	Appropriate skills	No	Appropriate Skills	Yes	Hyponasal	Yes	Mainstream School	Mild

37	M	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Moderate	Bilateral Type B	Yes	No	Yes	Severe	Yes	Severe	Yes	Hyponasal	No	Mainstream School	Mild
38	M	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Moderate	Bilateral Type B	Yes	No	Yes	Severe	Yes	Severe	Yes	Hyponasal	No	Special School	Moderate
39	M	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	No	Yes>No	Appropriate skills	Yes>No	Appropriate Skills	Yes	Hyponasal	No	Mainstream School	Severe
40	M	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Moderate	Bilateral Type B	Yes	Bifid Uvula	Yes>No	Severe>Appropriate skills	Yes>No	Severe>Appropriate Skills	Yes	No>Hyponasal	?ASD/Waiting Ax	Mainstream School	Mild
41	M	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	No	Yes	Severe	Yes	Severe	Yes	Mixed	?ASD/Waiting Ax	Mainstream School (special needs class)	-
42	F	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	No	-	-	-	-	Yes	No	Yes	Mainstream School	Mild
43	M	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	Bifid Uvula	Yes	Severe	Yes	Severe	Yes	Hyponasal	No	Mainstream School	-
44	M	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	No	-	-	-	-	Yes	Hyponasal	Yes	-	-
45	M	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	No	Yes	Severe	Yes	Severe	Yes	Hyponasal	Yes	Mainstream School	-
46	F	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	No	Yes	Moderate	Yes	Moderate	Yes	Hyponasal	No	Mainstream School	Moderate
47	F	c.758C>G	p.(Pro253Arg)	Appropriate	N/A	-	Bilateral Type A	No	No	Yes	Severe	Yes	Severe	Yes	Hyponasal	Yes	Special School	Severe
48	M	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Mild	-	Yes	Yes	Yes	Severe	Yes	Severe	Yes	Hypernasal	Yes	Mainstream School>Special School	Moderate
49	F	c.758C>G	p.(Pro253Arg)	Bilateral	-	-	-	Yes	Yes	No	Appropriate skills	No	Appropriate Skills	Yes	Hyponasal	No	-	Mild
50	F	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	Yes	Yes	Severe	Yes	Severe	Yes	Hypernasal	Yes	Special School	Mild
51	F	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	Yes	-	-	-	-	Yes	No	Yes	Mainstream School	Mild

52	M	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	No	Yes	-	Yes	-	Yes	Hyponasal	Yes	Mainstream School (special needs class)	Mild
53	F	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	No	Yes	Moderate	No	Appropriate Skills	Yes	Hyponasal	No	Mainstream School (additional support)	Mild
54	M	c.758C>G	p.(Pro253Arg)	Bilateral	Conductive	Mild	Bilateral Type B	Yes	Bifid Uvula	Yes	-	Yes	-	Yes	Hyponasal	?ASD/Waiting Ax	Special School	-