

Stuve-Wiedemann syndrome in one family: diagnosis and outcome.

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Objective:

This is a case report of one family with two live children affected by the autosomal recessive skeletal dysplasia Stuve-Wiedemann syndrome (SWS). This was initially considered to be a lethal skeletal dysplasia when first described mainly due to respiratory distress, feeding difficulties or hyperthermia. As the majority of SWS cases did not survive beyond infancy, a poor outlook was predicted. However, in our case both children did well in the neonatal period with the eldest child now surviving beyond the age of three years.

Case report:

Our patient had a normal first trimester scan at 13 weeks in her fourth pregnancy then had minimal antenatal input until her return at 38 weeks gestation, after moving abroad. Her first two pregnancies sadly resulted in early neonatal deaths: abroad with no medical details known. Fetal medicine review in her third pregnancy revealed severe short long bones with possible fractures. Appearances suggestive of skeletal dysplasia, but invasive testing was declined. Neonatal genetic testing confirmed Stuve-Wiedemann Syndrome. Karyotype confirmed the parents as carriers for the LIFR gene variant c.756dup, p.Lys253Ter, putting offspring at 25% risk of inheritance.

In the index pregnancy, the first fetal medicine scan at 38 weeks revealed short long bones with a curved appearance of both femora: suspicious of Stuve-Wiedemann Syndrome, like her previous child. Invasive testing was declined again. Post-natal skeletal survey showed characteristic bowing of tibia bilaterally consistent with SWS; confirmed by genetic analysis. The child is now 20 months old and doing well.

Discussion:

Stuve-Wiedemann Syndrome is a rare autosomal recessive skeletal dysplasia caused by a biallelic loss-of-function variant in the leukaemia inhibitory factor receptor (LIFR) gene. First described by Stuve and Wiedemann in 1971, it is considered to have significant mortality; few survive the first year. Cases are characterized by bowed long bones, joint restrictions, dysautonomia, respiratory and feeding issues.

Review of the literature found 31 reported cases of Stuve-Wiedemann syndrome who have survived infancy worldwide¹⁻¹⁴, all of these diagnosed postnatally, see table 1. Seventeen cases have a confirmed postnatal genetic mutation in the LIFR gene. To our knowledge this is the first report of antenatal diagnoses of two children with this rare syndrome in one family.



Figure 1: Antenatal ultrasound image of short and bowed femur at 38+6 weeks gestation

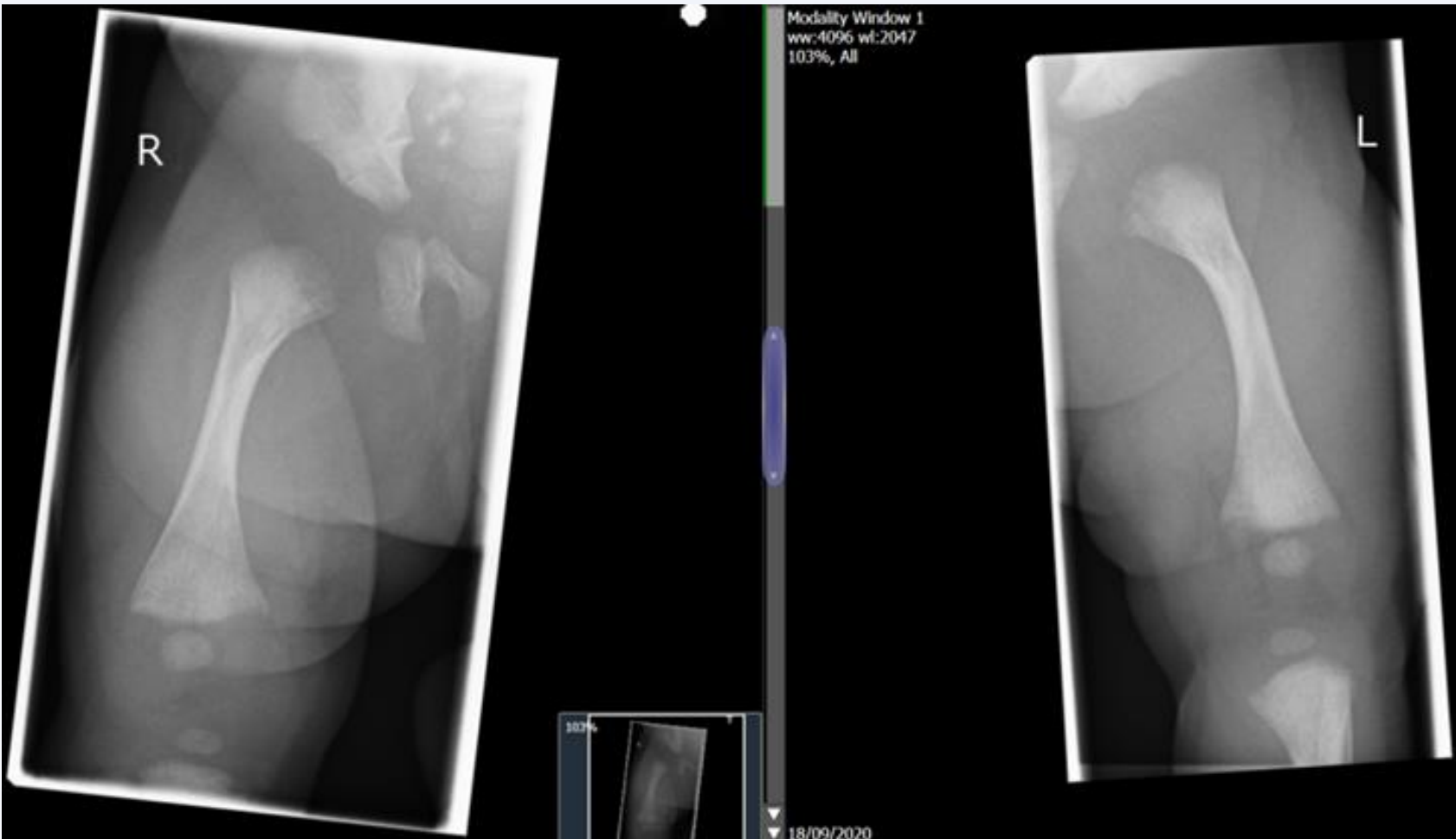
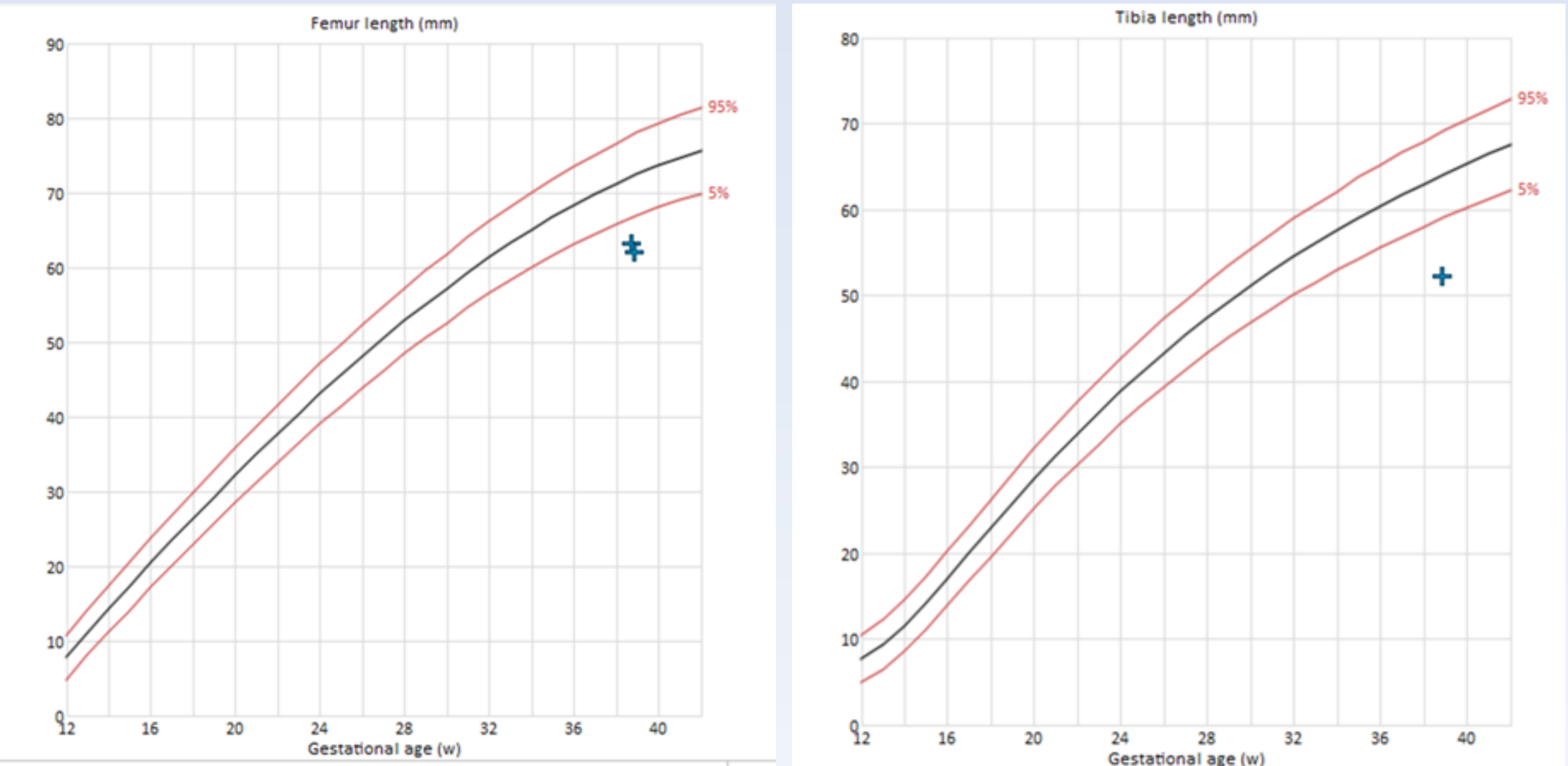
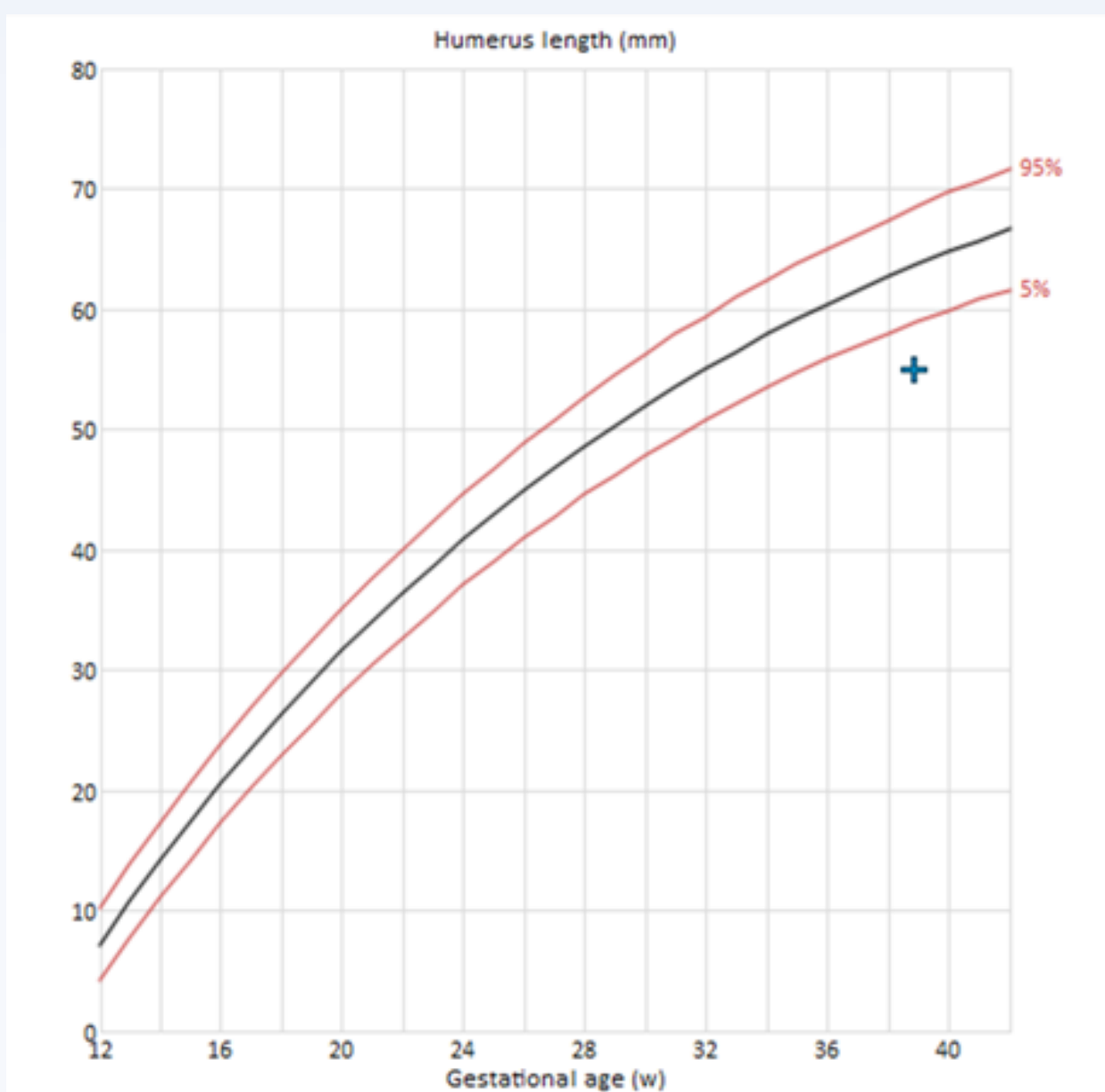


Figure 5: Postnatal X-Ray image of right and left femurs, demonstrating symmetrical bowing of the long bones



Figures 2,3 & 4: Antenatal ultrasound growth charts showing femur length, tibia length and humerus length all below the 5th centile for gestational age



Conclusions:

This case report is a useful addition to the literature and the growing argument that SWS is not necessarily lethal. As little is known about the plethora of rare skeletal dysplasias, the default counselling tends towards preparing parents for a poor outlook. Perhaps a more balanced approach to predicting prognosis and outcomes might be beneficial in such cases. Multidisciplinary input in an appropriate centre is vital for counselling and prognosis.

Paper	No. of cases	Antenatal (AN) or postnatal (PN) diagnosis	Clinical or genetic diagnosis	Genetic variant	Outcome
Yavuz et al 2021	1	PN	Genetic	Homozygous mutation LIFR gene	Alive and well aged 5
Alallah et al 2021	1	PN	Genetic	Novel pathogenic LIFR variant c.1387_1390del p.(Asn463Phefs*24)	Died at 31 months
Siccha et al 2020	4	PN	Genetic	2 novel heterozygous LIFR variants c.2259_2260del; p.(Gly754Leufs*18)	Well, aged 5. Attends normal school
		PN	Genetic	Homozygous pathogenic LIFR variant c.756dup; p.(Lys253*)	Motor milestones and expressive language delayed, aged 7
		PN	Genetic	Homozygous LIFR variant c.562_736del; p.(Val188Glyfs*15)	Global developmental delay and pureed diet required age 4
		PN	Genetic	Homozygous pathogenic LIFR variant c.756dup; p.(Lys253*)	Motor delay and mobility limitations age 12
Knipe et al 2015	1	PN	Genetic	Homozygous mutation LIFR gene, duplication in exon 3 at c.144_145dupGG	Alive and well age 15 months
Yesil et al 2014	3	PN	Genetic	Homozygous substitution in LIFR exon 15 c.2074C>T (p.Arg692X)	Alive age 4.5
		PN	Genetic	Homozygous substitution in LIFR exon 15 c.2074C>T (p.Arg692X)	Alive age 6
		PN	Genetic	Homozygous substitution in LIFR exon 15 c.2074C>T (p.Arg692X)	Alive age 2
Buonuomo et al 2014	1	PN	Genetic	Homozygous mutation exon 7 LIFR gene 5p13-p12	Alive age 9
Jung et al 2010	10	No details	Genetic	LIFR variant c.875T>C c.1438-4A>G	Alive age 14
		No details	Genetic	LIFR variant c.2434C>T c.2434C>T	Alive age 36 months
		No details	Genetic	LIFR variant c.756_757insT c.756_757insT	Alive age 6
		No details	Genetic	LIFR variant c.1789C>T c.1789C>T	Alive age 9
		No details	Genetic	LIFR variant c.1252C>T c.1252C>T	Alive age 5.5
		No details	Genetic	LIFR variant c.380_381insT c.2336G>T	Alive age 5
		No details	Clinical	-	Alive age 12
		No details	Clinical	-	Alive age 5.5
		No details	Clinical	-	Alive age 8
		No details	Clinical	-	Died age 6
Bonthuis et al 2009	1	PN	Genetic	167-170delTAAC in exon 3 and C1865T in exon 13 of LIFR gene	Alive age 3
Gaspar et al 2008	1	PN	Genetic	Homozygous deletion exon 3 LIFR gene c.167_170delTAAC	Alive age 12
Di Rocco et al 2003	2	PN	Clinical	-	Alive age 12
		PN	Clinical	-	Alive age 3
Al Gazali et al 2003	3	PN	Clinical	-	Alive age 6
		PN	Clinical	-	Alive age 2.8
		PN	Clinical	-	Alive age 2
Chen et al 2001	1	PN	Clinical, genetic testing performed	Supernumary marker chromosome mosaicism derived from chromosome 5, significance unknown	Alive age 7
Superti-Furga et al 1998	2	PN	Clinical	-	Alive age 10
		PN	Clinical	-	Alive age 7

References:

1. Gaspar IM, Saldanha T, Cabral P, Vilhena MM, Tuna M, Costa C, Dagoneau N, Daire VC, Hennekam RC. Long-term follow-up in Stuve-Wiedemann syndrome: a clinical report. Am J Med Genet A. 2008 Jul 1;146A(13):1748-53
2. Al-Gazali L, Ravenscroft A, Feng A, Shubbar A, Al-Saggaf A, Haas D. Stüve-Wiedemann syndrome in children surviving infancy: clinical and radiological features. Clinical Dysmorphology. 2003;12(1):1-8
3. Siccha SM, Cueto AM, Parrón-Pajares M, González-Morán G, Pacio-Míguez M, Del Pozo Á et al. Delineation of the clinical and radiological features of Stuve-Wiedemann syndrome childhood survivors, four new cases and review of the literature. Am J Med Genet 2021 Mar;185(3):856-865
4. Jung C, Dagoneau N, Baujat G, Le Merrer M, David A, Di Rocco M et al. Stuve-Wiedemann syndrome: long-term follow-up and genetic heterogeneity. Clin Genet 2010 Mar;77(3):266-72
5. Artibeiro V, Portela F, Reis AT. Anesthesia for Stüve-Wiedemann syndrome: a rare adult patient case report. J Appl Genet. 2020 Dec;61(4):571-573
6. Knipe M, Stanbury R, Unger S, Chakraborty M. Stuve-Wiedemann syndrome with a novel mutation. BMJ Case Rep. 2015 Aug 30;2015:bcr2015212032
7. Yesil G, Lebre AS, Santos SD, Güran O, Özahi I, Daire VC, Güran T. Stuve-Wiedemann syndrome: is it underrecognized? Am J Med Genet A. 2014 Sep;164A(9):2200-5
8. Buonuomo PS, Macchiaiolo M, Cambiaso P, Rana I, Digilio MC, Bartuli A. Long-term follow-up in Stuve-Wiedemann syndrome: a case report with articular involvement. Clin Dysmorphol. 2014 Apr;23(2):45-6
9. Bonthuis D, Morava E, Booi LH, Driessen JJ. Stuve Wiedemann syndrome and related syndromes: case report and possible anesthetic complications. Paediatr Anaesth. 2009 Mar;19(3):212-7
10. Di Rocco M, Stella G, Bruno C, Doria Lamba L, Bado M, Superti-Furga A. Long-term survival in Stuve-Wiedemann syndrome: a neuro-myo-skeletal disorder with manifestations of dysautonomia. Am J Med Genet A. 2003 May 1;118A(4):362-8
11. Chen E, Cotter PD, Cohen RA, Lachman RS. Characterization of a long-term survivor with Stüve-Wiedemann syndrome and mosaicism of a supernumerary marker chromosome. Am J Med Genet. 2001 Jul 1;101(3):240-5
12. Superti-Furga A, Tenconi R, Clementi M, Eich G, Steinmann B, Boltshauser E, Giedion A. Schwartz-Jampel syndrome type 2 and Stüve-Wiedemann syndrome: a case for "lumping". Am J Med Genet. 1998 Jun 30;78(2):150-4
13. Alallah J, Alamoudi LO, Makki RM, Shawli A, AlHarbi AT. Stuve-Wiedemann syndrome with a novel mutation in a Saudi infant. International Journal of Pediatrics and Adolescent Medicine. 2021 Oct 9. <https://doi.org/10.1016/j.ijpam.2021.10.002> <https://doi.org/10.1016/j.ijpam.2021.10.002>. Epub ahead of print
14. Ozkale Yavuz O, Yildiz AE, Aydingoz U. Atypical medial femoral condylar fracture in Stuve-Wiedemann syndrome. Clin Dysmorphol. 2021 Nov 12. doi: 10.1097/MCD.0000000000000400. Epub ahead of print