Title: Ritscher-Schinzel Syndrome *GeneReview* – Establishing the Molecular Basis of RSS: A Timeline
Authors: Elliott AM, Chudley A
Initial posting: January 2020

Establishing the Molecular Basis of RSS: A Timeline

Ritscher et al [1987] described two sisters with the characteristic craniofacial anomalies, A-V canal (complete and incomplete) malformations of the heart and posterior fossa malformations (cerebellar vermis hypoplasia and Dandy-walker malformation) and mild developmental delay. They suggested autosomal recessive inheritance. Launener et al [1989] followed the younger surviving sibling reported in Ritscher et al [1987] and suggested that the presence of a humoral immunodeficiency may be a manifestation of the syndrome. Dandy-Walker malformation with communicating hydrocephalus, aplasia of the posterior portion of the cerebellar vermis, and high insertion of the confluent sinus. In the other sister, a Dandy-Walker variant was found with aplasia of the cerebellar vermis and hypoplasia of the hemispheres, large cisterna magna, high insertion of the confluent sinus, but no hydrocephalus.

Verloes et al [1989] reported on a third case with a similar constellation of clinical findings to those described by Ritscher et al [1987]. These authors suggested the syndrome names of cranio-cerebello-cardiac dysplasia or (3C) and/or Ritscher-Schinzel syndrome.

Marles et al [1995] reported on eight children from Northern Manitoba with RSS and because of consanguinity and some affected children being related as cousins that autosomal recessive inheritance was likely the mode of inheritance.

Leonardi et al [2001] reported cases and reviewed the literature on RSS and proposed diagnostic criteria.

Elliott et al [2013] reported on 11 individuals with RSS from Manitoba and Northwestern Ontario (including 4 who were previously report by Marles et al [1995] and identified biallelic pathogenic variants in *KIAA0196* (now termed *WSHC5*) in all affected individuals.

Kolanaczyk et al [2015] reported on two brothers with a phenotype that overlaps with RSS and identified a hemizygous missense variant in the *CCDC22* on the X chromosome suggesting genetic heterogeneity in RSS.

References

Elliott AM, Simard LR, Coghlan G, Chudley AE, Chodirker BN, Greenberg CR, Burch T, Ly V, Hatch GM, Zelinski T. A novel mutation in KIAA0196: identification of a gene involved in Ritscher–Schinzel/3C syndrome in a First Nations cohort. J Med Genet. 2013;50:819-22.

Kolanczyk M, Krawitz P, Hecht J, Hupalowska A, Miaczynska M, Marschner K, Schlack C, Emmerich D, Kobus K, Kornak U, Robinson PN, Plecko B, Grangl G, Uhrig S, Mundlos S, Horn D. Missense variant in

CCDC22 causes X-linked recessive intellectual disability with features of Ritscher-Schinzel/3C syndrome. Eur J Hum Genet. 2015;23:633-8.

Lauener R, Seger R, Jorg W, Halle F, Aeppli R, Schinzel A. Immunodeficiency associated with Dandy-Walker-like malformation, congenital heart defect, and craniofacial abnormalities. Am J Med Genet. 1989;33:280-1.

Leonardi ML, Pai GS, Wilkes B, Lebel RR. Ritscher-Schinzel cranio-cerebello-cardiac (3C) syndrome: report of four new cases and review. Am J Med Genet. 2001;102:237-42.

Marles SL, Chodirker BN, Greenberg CR, Chudley AE. Evidence for Ritscher-Schinzel syndrome in Canadian Native Indians. Am J Med Genet. 1995;56:343-50.

Ritscher D, Schinzel A, Boltshauser E, Briner J, Arbenz U, Sigg P. Dandy-Walker(like) malformation, atrio-ventricular septal defect and a similar pattern of minor anomalies in 2 sisters: a new syndrome? Am J Med Genet. 1987;26:481-91.

Verloes A, Dresse M, Jovanovic M, Dodinval P, Geubelle F. 3C syndrome: third occurrence of cranio-cerebello-cardiac dysplasia (Ritscher-Schinzel syndrome). Clin Genet. 1989;35:205-8.