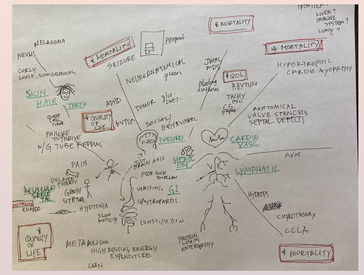
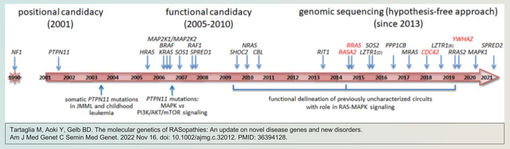
UNMET NEEDS IN RASOPATHIES

RASOPATHIES NET.ORG
Beth Stronach PhD
Lisa Schoyer MFA



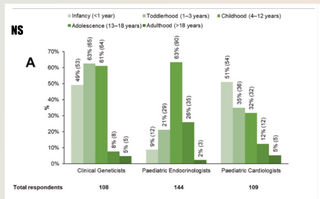
TIMELINE OF GENE DISCOVERY AND ASSOCIATION



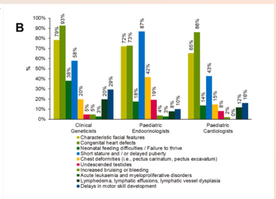
Tartaglia M, Aoki Y, Gelb BD. The molecular genetics of RASopathies: An update on novel disease genes and new disorders. Am J Med Genet C Semin Med Genet. 2022 Nov 16. doi: 10.1002/ajmg.c.32012. PMID: 36394128.

RASOPATHIES PREVALENCE AND GENE ASSOCIATIONS

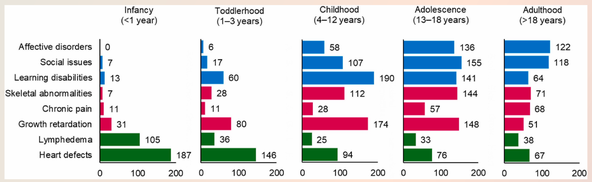
CLINICAL DIAGNOSIS



How frequently are patients referred to you from each age group for Noonan syndrome?
n = 361 (99%) respondents. Physicians could select from the following choices for the five age groups: 'Never', 'Very Seldom', 'Occasionally', 'Frequently' and 'Most'. Shown are the results of merging 'Frequently' and 'Most' for each age group (% [n]).



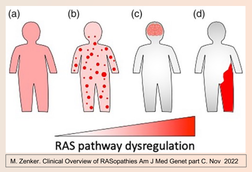
In your experience, how frequently are the following characteristics a leading cause for a clinical diagnosis of Noonan syndrome?
n = 362 (99%) respondents. Physicians could select from the following choices for each characteristic: 'Never', 'Very Seldom', 'Occasionally', 'Frequently' and 'Most'. Shown are the results of merging 'Frequently' and 'Most' for each age group (% [n]).



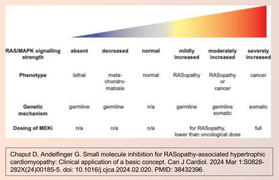
What are the most important factors in each age group that affect quality of life in patients with Noonan syndrome?
n = 242 (66%) physicians for affective disorders/social issues/learning disabilities (blue), skeletal/pain/growth (pink) and lymphedema/heart (green). Note that respondents could provide answers in one or more categories.

Garcia-Miñaur S, Burkitt-Wright E, Verloes A, Shaikh G, Lebl J, Östman-Smith I, Wolf CM, Ortega Castelló E, Tartaglia M, Zenker M, Edouard T. European Medical Education Initiative on Noonan syndrome: A clinical practice survey assessing the diagnosis and clinical management of individuals with Noonan syndrome across Europe. Eur J Med Genet. 2022 Jan;65(1):104371. doi: 10.1016/j.ejmg.2021.104371. Epub 2021 Oct 29. PMID: 34757053.

BREADTH OF RAS/MAPK CONDITIONS



M. Zenker. Clinical Overview of RASopathies Am J Med Genet part C. Nov 2022



Chaput D, Andelfinger G. Small molecule inhibition for RASopathy-associated hypertrophic cardiomyopathy: Clinical application of a basic concept. Can J Cardiol. 2024 Mar 1:S0828-282X(24)00185-5. doi: 10.1016/j.cjca.2024.02.020. PMID: 38432396.

Class	Diagnostic entities
Noonan syndrome and related disorders	Noonan syndrome, cardiofaciocutaneous syndrome, Costello syndrome, Noonan syndrome with multiple lentigines, Noonan syndrome-like disorder with loose anagen hair, CBL syndrome
Neurofibromatosis type 1 and related disorders	Neurofibromatosis type 1, Legius syndrome, schwannomatosis
"Nonsystemic" RASopathies	Autosomal dominant intellectual disability type 5 (SYNGAP1 syndrome), RASA1-related capillary malformation-arteriovenous malformation syndrome (CM-AVM)
Mosaic RASopathies	Nevus sebaceous syndrome/ Schimmelpenning–Feuerstein–Mims syndrome, keratinocytic epidermal nevus (syndrome), congenital melanocytic nevus/neurocutaneous melanosis, oculocerebrocranial syndrome, vascular malformations with and without regional overgrowth and others

Mosaic RASopathies

	Gene	Features
Nevus sebaceous	HRAS, KRAS, NRAS	-
Keratinocytic epidermal nevi	HRAS, KRAS, NRAS	-
Melanocytic nevi	HRAS, NRAS	-
Nevus spilus	HRAS, NRAS	-
Woolly hair nevus	HRAS, NRAS	-
Melorheostosis	MAP2K1, KRAS	Sclerosing bone dysplasia
Lymphatic anomalies	SOS1, KRAS, ARAF, BRAF, NRAS, CBL	-
Vascular malformations	KRAS, NRAS, BRAF, MAP2K1, RASA1	Low flow and arteriovenous malformations
Juvenile myelomonocytic leukemia	PTPN11, CBL, NF1, NRAS, KRAS	-
RAS-associated autoimmune leuloproliferation	NRAS, KRAS	Autoimmunity and lymphoproliferation
Epidermal nevus syndromes (ENS)	HRAS, KRAS, NRAS	Epidermal nevi, eyes, skeletal, CNS anomalies
Schimmelpenning-Feuerstein-Mims syndrome (SFMS)	HRAS, NRAS, KRAS	Sebaceous nevi, brain, eye and skeletal abnormalities
Cutaneous skeletal hypophosphatemia syndrome (CSHS)	HRAS, NRAS	Epidermal nevi, melanocytic nevi, hypophosphatemia
Keratinocytic epidermal nevus syndrome (KENS)	KRAS	Keratinocytic nevi, brain, eye and skeletal abnormalities
Phacomatosis pigmentokeratotica (PPK)	HRAS, KRAS, BRAF	Speckled lentiginous and sebaceous nevus, brain, eye, skeletal abnormalities
Encephalocraniocutaneous lipomatosis (ECCL)	KRAS, NRAS	Ocular anomalies, skin lesions, CNS anomalies
Oculo-ectodermal syndrome (OES)	KRAS	epibulbar dermoids, aplasia cutis congenita
Gorham–Stout disease	KRAS	Osteolysis, lymphatic vessels proliferation
Others	PTPN11	lateralized overgrowth, vascular malformation

Carli D, Resta N, Ferrero GB, Ruggieri M, Mussa A. Mosaic RASopathies: A review of disorders caused by somatic pathogenic variants in the genes of the RAS/MAPK pathway. Am J Med Genet C Semin Med Genet. 2022 Dec;190(4):520-529. PMID: 36461154.

CLINICAL RED FLAGS

Table 1
Clinical red flags for RASopathies Lioncino et al. Heart Failure Clin 18 (2022) 19–29 https://doi.org/10.1016/j.hfc.2021.07.004

Facial features	NS: broad forehead, down slanting palpebral fissures, hypertelorism, low set ears, pterygium colli, epicanthal folds, short and depressed nasal root CS: hypertelorism, down slanting palpebral fissures. Facial features are coarser. Feeding and suction difficulties are more prevalent. CFCS: macrocephaly, bitemporal narrowing, coarse facial features, small curly friable hair with sparse eyebrows with hyperkeratosis (ulerythema ophryogenes), broad nasal base, wide labial philtrum. Coarser than NS
Cardiovascular	Pulmonary valve stenosis, hypertrophic cardiomyopathy, mitral valve dysplasia, atrial septal defect, ventricular septal defect, atrioventricular septal defect, aortic coarctation, coronary arteries abnormalities
Electrocardiography	Extreme right-axis deviation (north west axis), left or right bundle branch block (NSML), prolonged QT (NSML), repolarization abnormalities, multifocal atrial tachyarrhythmia (CS)
Musculoskeletal	Short stature, hypotonia (CFCS), Pes planus (CFCS), scoliosis, pectus deformity, hip dysplasia, osteopenia/osteoporosis
Dermatologic	Cafè-au-lait spots, papillomas (CS), palmar keratoderma, acanthosis nigricans, keratosis pilaris (CFC), ulerythema ophryogenes (CFC), lentigines (NSML), multiple pigmented nevi
Genitourinary	Cryptorchidism, transitional cell carcinoma of the urinary bladder (CS)
Hematopoietic	Easy bruising, von Willebrand disease, coagulation defects, thrombocytopenia, NS/myeloproliferative disease (leukocytosis with monocytosis, thrombocytopenia, and hepatosplenomegaly)
Gastrointestinal	Failure to thrive, gastroesophageal reflux, intestinal malrotation, pyloric stenosis
Sensorineural	Hearing loss, laryngomalacia, cataract, strabismus
Neurologic	Seizures, infantile spasms, hydrocephalus, Chiari I malformation, intellectual disability
Endocrine	Growth hormone deficiency, hypoglycemia, delayed puberal spurt, short stature
Oncology	Juvenile myelomonocytic leukemia, lymphedema

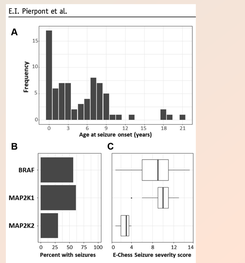
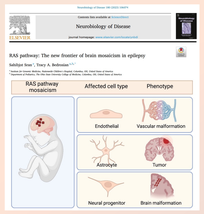
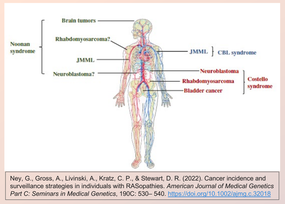


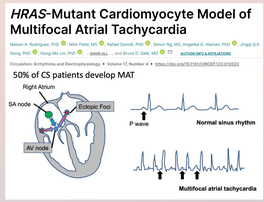
Figure 1 Characteristics of epilepsy in CFC syndrome. A. Histogram depicting age of onset of seizures among 76 individuals with CFC syndrome. B-C. Frequency and severity of epilepsy based on the affected gene. CFC, cardiofaciocutaneous; E-Chess, Early Childhood Epilepsy Severity Scale.

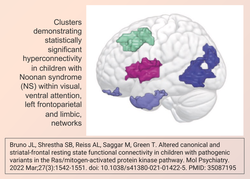
Pierpont, Elizabeth I. et al. Neurologic and neurodevelopmental complications in cardiofaciocutaneous syndrome are associated with genotype: A multinational cohort study. 2022 Genetics in Medicine, Volume 24, Issue 7, 1556 - 1566





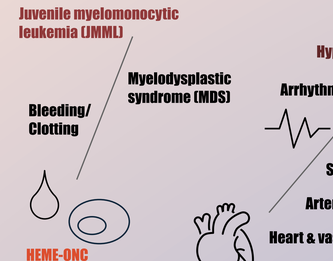
Ney, G., Gross, A., Livinski, A., Kratz, C. P., & Stewart, D. R. (2022). Cancer incidence and surveillance strategies in individuals with RASopathies. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, 190C: 530– 540. https://doi.org/10.1002/ajmg.c.32018

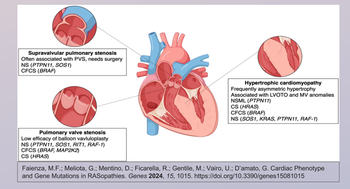




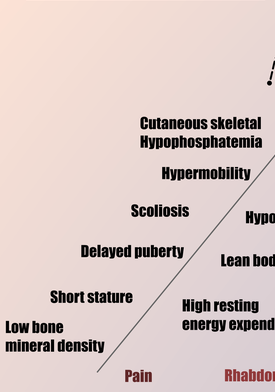
Clusters demonstrating statistically significant hyperconnectivity in children with Noonan syndrome (NS) within visual, ventral attention, left frontoparietal and limbic, networks

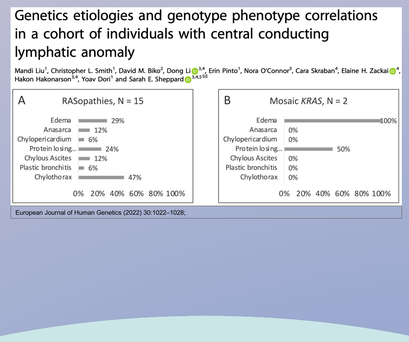
Bruno JL, Shrestha SB, Reiss AL, Saggar M, Green T. Altered canonical and striatal-frontal resting state functional connectivity in children with pathogenic variants in the Ras/mitogen-activated protein kinase pathway. Mol Psychiatry. 2022 Mar;27(3):1542-1551. doi: 10.1038/s41380-021-01422-5. PMID: 35087195





Faienza, M.F.; Meliota, G.; Mentino, D.; Ficarella, R.; Gentile, M.; Vairo, U.; D'amato, G. Cardiac Phenotype and Gene Mutations in RASopathies. *Genes* **2024**, *15*, 1015. https://doi.org/10.3390/genes15081015





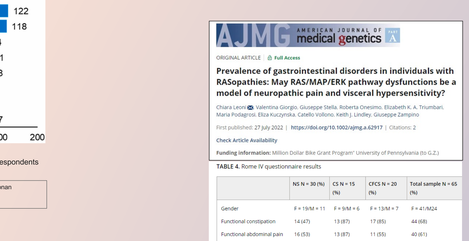


TABLE 4. Rome IV questionnaire results

	NS N = 30 (%)	CS N = 15 (%)	CFCS N = 20 (%)	Total sample N = 65 (%)
Gender	F = 19/M = 11	F = 9/M = 6	F = 13/M = 7	F = 41/M24
Functional constipation	14 (47)	13 (87)	17 (85)	44 (68)
Functional abdominal pain	16 (53)	13 (87)	11 (55)	40 (61)
Aerophagia	2 (7)	3 (20)	15 (75)	20 (31)
Irritable bowel syndrome	2 (7)	3 (20)	3 (15)	8 (12)
Functional dyspepsia	0	0	1 (5)	1 (2)
Abdominal migraine	2 (7)	0	1 (5)	3 (5)
Non retentive fecal incontinence	0	0	2 (10)	2 (3)
Cyclic vomiting	0	1 (6)	0	1 (2)

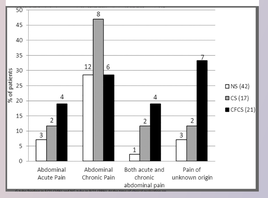


Table 1. Prevalence of feeding problems in the first year of life in patients with NS with the most prevalent gene mutations.

	PTPN11	*SOS1*	*RAF1*
Digillio et al., 2012 [9]	13/20 = 65%	0/8 = 0%	3/4 = 75%
Draaisma et al., 2020 [15]	36/63 = 57%	6/16 = 37.5%	2/4 = 50%

Tiemens, D.K., van Haaften, L., Leenders, E., van Wegberg, A.M.J., Gunther Moor, B., Geelen, J., Draaisma, J.M.T. Feeding Problems in Patients with Noonan Syndrome: A Narrative Review. *J. Clin. Med.* **2022**, *11*,754.

TOOLS FOR COLLECTING OUTCOMES

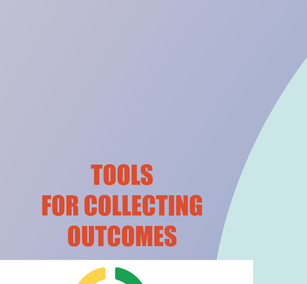
EUROPEAN RASOPATHIES
Patient Registry

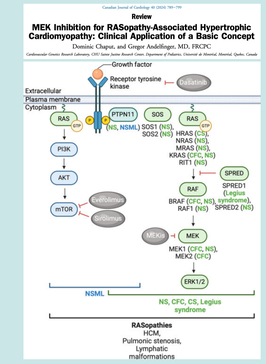
NIH NATIONAL CANCER INSTITUTE
RASopathies Study Newsletter Winter 2022-23
Division of Cancer Epidemiology and Genetics - Clinical Genetics Branch
Natural History Study

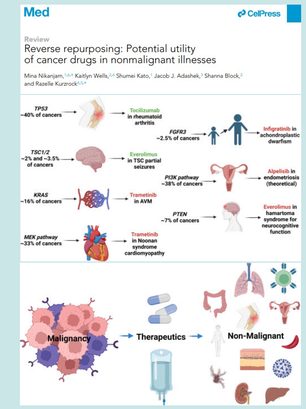
CDRC
CURE DRUG REPURPOSING COLLABORATORY

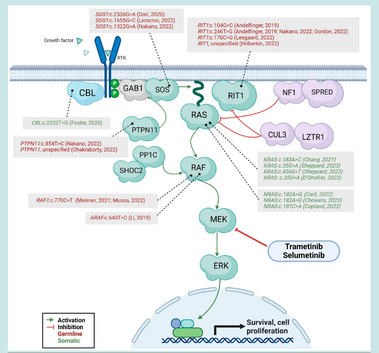
CURE ID
Challenging cases... New approaches
Treatment Registry

THERAPEUTIC POSSIBILITIES

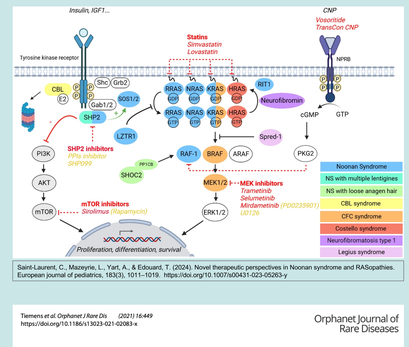








Gazzin A, Fornari F, Cardaropoli S, Carli D, Tartaglia M, Ferrero GB, Mussa A. *Exploring New Drug Repurposing Opportunities for MEK Inhibitors in RASopathies: A Comprehensive Review of Safety, Efficacy, and Future Perspectives of Trametinib and Selumetinib*. Life. 2024; 14(6):731. https://doi.org/10.3390/life14060731



Saint-Laurent, C., Mazeyrie, L., Yart, A., & Edouard, T. (2024). Novel therapeutic perspectives in Noonan syndrome and RASopathies. European journal of pediatrics, 183(3), 1011–1019. https://doi.org/10.1007/s00431-023-05263-y

Tiemens *et al. Orphanet J Rare Dis (2021) 16:449* https://doi.org/10.1186/s13023-021-02083-x

Orphanet Journal of Rare Diseases

REVIEW Open Access

Patient engagement in the design of clinical research in Noonan syndrome spectrum disorders: a scoping review

Dagmar K. Tiemens[1,6], Jacqueline Nugteren[1], Erika Leenders[2], Ellen Wingbermühle[2,3,4], Carina A. C. M. Pittens[5] and Jos M. Th. Draaisma[1*]