SSBP Syndrome Sheets

Noonan Syndrome

First description
The first description of Noonan syndrome (NS) dates back to 1883, when a student named Kobylinski reported on a male patient with several phenotypical characteristics. In 1963, paediatric cardiologists Dr. Jacqueline Noonan and Dorothy Ehmke were the first to identify NS as a distinct syndrome in both male and female patients, with congenital heart defects, small stature, typical faces, skeletal malformations and mild developmental delay (Noonan & Ehmke, 1963; Noonan, 1968). John Opitz, one of Dr. Noonan's students, suggested the eponym and confirmed NS as a nosologic entity.

Associated conditions
NS is a genetic multisystem disorder caused by a pathogenic variant in genes encoding for components of the Ras-MAPK signaling pathway. Syndromes with shared pathogenetic mechanisms and clinical overlap with NS include Noonan syndrome with multiple lentigines (NSML; formerly called LEOPARD syndrome), Noonan-like syndrome with loose anagen hair (NSLH; also called Mazzanti syndrome), Noonan syndrome-like disorder (also called CBL syndrome), Cardiofaciocutaneous syndrome (CFC), Costello syndrome (CS), Legius syndrome (LS), and neurofibromatosis type 1 (NF1). These syndromes are part of a larger group of related conditions known as RASopathies (Tartaglia et al., 2011; Tajan et al., 2018).

Genetics and molecular biology
NS is most often inherited in an autosomal dominant manner, although NS also can be inherited in an autosomal recessive manner. In 60% of patients with autosomal dominant NS, the condition is caused by a de novo mutation. In approximately 50% of patients with NS a missense mutation is found in the PTPN11 gene on chromosome 12 (12q24.13). Germline mutations in more than 14 additional genes involved in the RAS-MAPK pathway have been associated with NS. These genes include SOS1 (10-13% of the cases), RAF1 (5-10%), RIT1 (5%), LZTR1, KRAS, NRAS, MRAS, BRAF, CBL, SOS2, RRAS, RRAS2, MAP2K1, and MAP2K2. In about 20% of the patients with a clinical diagnosis of NS, no variation in the abovementioned genes can yet be found (Allanson & Roberts, 2019; Grant et al., 2018; Liao & Mehta, 2019; Motta et al., 2020; Tartaglia et al., 2022; Zenker, 2022).

Incidence/prevalence
The incidence of NS is estimated between 1 in 1000 to 1 in 2500 live births (Roberts et al., 2013).

Physical features and natural history
Key characteristics are 1) short stature, 2) typical facial dysmorphology (wide-spread and down-slanting eyes, drooping eyelids, and low-set, posteriorly rotated ears with a thickened helix), and 3) congenital heart defects (pulmonary valve stenosis, hypertrophic cardiomyopathy, and atrial septal defects are most common). Some additional features are variable developmental delay, neonatal feeding difficulties, failure to thrive, hematologic and ectodermal anomalies, skeletal

anomalies (e.g., chest deformity), lymphatic diseases, cryptorchidism, ocular abnormalities, widely spaced nipples, and a webbed neck.

Neurological complications are relatively uncommon in patients with NS, however, conditions such as hydrocephalus and Chiari type I malformations are described. Epilepsy is also slightly more prevalent compared to the general population. Pain is a common complaint in patients with NS and can sometimes be characterised as neuropathic pain (Draaisma et al., 2024; Leoni et al., 2019).

Life expectancy for patients with NS is fairly normal, unless there are major complications of heart or lymphatic disease. Premature delivery is the main source of morbidity.

It should be noted that phenotypical expression is highly variable in NS and physical characteristics are often milder in adulthood than in childhood. The diagnosis is primarily made on clinical grounds, by observation of cardinal features (Allanson & Roberts, 2019; Noonan, 2005). The most widely used scoring system was developed in 1994 and updated and validated in 2010 (Van der Burgt et al.,1994; DYSCERNE-Noonan Syndrome Guideline Development Group, 2010).

Brain structure and function

Research on brain structure and function in patients with NS is still emerging, but current findings suggest increased connectivity in the visual, ventral attention, left frontoparietal, and limbic networks in children with NS compared to typically developing peers. This hyperconnectivity may contribute to impairments in inhibition, attention, and orientation (Bruno et al., 2022). In a separate study examining brain structures, children with NS were found to have smaller volumes in areas of the corpus striatum - specifically the caudate, putamen, and pallidum - when compared to typically developing children. These brain structures are involved in motivation, motor and action planning, decision-making, and reinforcement processes. A smaller corpus striatum is often associated with inattention and hyperactivity, problems which are frequently seen in children with NS (Johnson et al., 2019).

Behavioural characteristics and psychopathology

There is evidence of an increased risk of behavioural problems in children, primarily characterised by social problems (e.g., problems in understanding social situations, articulating and explaining social experiences, problems in connecting with peers), inattention, hyperactivity, impulsivity and problems in emotion regulation (Alfieri et al., 2021; Pierpont, 2016; Pierpont et al., 2018). Internalising problems, characteristics of autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are more prevalent than in the general population (McNeill et al., 2019; Pierpont, 2016). Externalising problems are also reported in children with NS, but they are less common than internalising problems (Alfieri et al., 2014; Pierpont, 2016). In adults with NS, there are indications that internalising problems and social distress are more common (Pierpont 2016; Wingbermühle et al., 2012a, 2022). Higher levels of introversion and alexithymia (i.e., difficulty identifying and verbalising one's own emotions) in adults with NS may contribute to this internalising symptomatology (Roelofs et al., 2019; Wingbermühle et al., 2022).

Neuropsychological characteristics

Intelligence scores show a wide range, with a mildly lowered average intelligence. Intellectual disability (IQ < 70) is present in less than a quarter of patients with NS. No specific or consistent cognitive impairments are found in patients with NS at the group level, when general intelligence or educational level are taken into account (Naylor et al., 2023; Wingbermühle et al., 2022). However, cognitive weaknesses have been identified in various studies. In children, language and motor development are frequently delayed. Research has identified a highly variable cognitive profile in children with NS, with evidence of weaknesses in visual processing, language development, working memory, attention, and planning and organisational skills. These cognitive weaknesses likely contribute to learning problems, which are frequently reported in children with NS, and the need for special education in a number of cases (Kramer et al., 2025; Pierpont 2016). While cognitive weaknesses are frequent in childhood, in adulthood only a lowered speed of information processing and slight problems in emotion recognition are described, although patients report executive function problems in daily life (Wingbermühle et al., 2012a, 2012b).

Available guidelines for assessment/treatment/management

The specific problems that patients with NS may encounter in daily life appear to result from a complex interaction between genetic, somatic, cognitive, psychological, and environmental factors. Therefore, a multidisciplinary approach and intensive collaboration between clinical geneticists, cardiologists, paediatricians, clinical neuropsychologists, physiotherapists, and speech therapists, among others, is necessary to treat patients with NS as best as possible. Moreover, NS is a lifelong developmental disorder, which poses different challenges in different stages of life. Repeated clinical and neuropsychological assessments are recommended throughout the lifespan, particularly at key developmental stages (e.g., before entering primary school and secondary school, and in the transition to adulthood) and when difficulties arise. Based on these assessments, targeted interventions can be provided, such as individualised educational accommodations, psychological therapy or psychiatric treatment. The recommended multidisciplinary approach and life-long follow-up may be formalised in centres of expertise for patients with NS and other RASopathies. Specific recommendations for the management of patients with NS at different stages of their lives can be found in the international clinical guidelines on Management of Noonan syndrome from the Noonan Syndrome Guideline Development Group (DYSCERNE, 2010). A revised edition will be published in the near future.

Useful websites/associations for more information

www.dyscerne.org/dysc/Guidelines - For the Noonan Syndrome Clinical Management Guidelines.

www.ncbi.nlm.nih.gov/omim/163950 - For the information on NS in OMIM, an online database of human genes and genetic disorders.

www.noonansyndrome.org.uk - For the Noonan syndrome support group Inc.

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References

1. Alfieri, P., Cumbo, F., Serra, G., Trasolini, M., Frattini, C., Scibelli, F., Licchelli, S., Cirillo, F., Caciolo, C., Casini, M. P., D'Amico, A., Tartaglia, M., Digilio, M. C., Capolino, R., & Vicari, S. (2021). Manic and depressive symptoms in children diagnosed with Noonan syndrome. Brain Sciences, 11(2), 233. https://doi.org/10.3390/brainsci11020233
2. Alfieri, P., Piccini, G., Caciolo, C., Perrino, F., Gambardella, M. L., Mallardi, M., Cesarini, L., Leoni, C., Leone, D., Fossati, C., Selicorni, A., Digilio, M. C., Tartaglia, M., Mercuri, E., Zampino, G., & Vicari, S. (2014). Behavioral profile in RASopathies. American journal of medical genetics. Part A, 164A(4), 934-942. https://doi.org/10.1002/ajmg.a.36374
3. Allanson, J. E., & Roberts, A. E. (2019). Noonan Syndrome. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, K. Stephans, & A. Amemiya (Eds.), GeneReviews®. University of Washington. https://www.ncbi.nlm.nih.gov/books/NBK1124/
4. Bruno, J. L., Shrestha, S. B., Reiss, A. L., Saggar, M., & Green, T. (2022). Altered canonical and striatal-frontal resting state functional connectivity in children with pathogenic variants in the Ras/mitogen-activated protein kinase pathway. Molecular psychiatry, 27(3), 1542-1551. https://doi.org/10.1038/s41380-021-01422-5
5. Draaisma, F., Leenders, E. K. S. M., Erasmus, C. E., Braakman, H. M. H., Burgers, M. C. J., Coppens, C. H., Rinne T., Zenker M., Tartaglia M., Reintjes W., Voermans N. C., van Engelen B. G. M., van Alfen N., & Draaisma, J. M. T. (2024). Nerve enlargement in patients with Noonan syndrome: A retrospective cohort study. American Journal of Medical Genetics Part A, 194(11), e63810. https://doi.org/10.1002/ajmg.a.63810
6. DYSCERNE-Noonan Syndrome Guideline Development Group. (2010). Management of Noonan syndrome: A clinical guideline [Update expected 2025]. University of Manchester. https://rasopathiesnet.org/wp-content/uploads/2014/01/265_Noonan_Guidelines.pdf
7. Grant, A. R., Cushman, B. J., Cavé, H., Dillon, M. W., Gelb, B. D., Gripp, K. W., Lee, J. A., Mason-Suares, H., Rauen, K. A., Tartaglia, M., Vincent, L. M., & Zenker, M. (2018). Assessing the gene-disease association of 19 genes with the RASopathies using the ClinGen gene curation framework. Human Mutation, 39(11),1485-1493. https://doi.org/10.1002/humu.23624
8. Johnson, E. M., Ishak, A. D., Naylor, P. E., Stevenson, D. A., Reiss, A. L., & Green, T. (2019). PTPN11 Gain-of-Function Mutations Affect the Developing Human Brain, Memory, and Attention. Cerebral cortex, 29(7), 2915-2923. https://doi.org/10.1093/cercor/bhy158
9. Kent, O. A., Saha, M., Coyaud, E., Burston, H. E., Law, N., Dadson, K., Chen, S., Laurent, E. M., St-Germain, J., Sun, R. X., Matsumoto, Y., Cowen, J., Montgomery-Song, A., Brown, K. R., Ishak, C., Rose, J., De Carvalho, D. D., He, H. H., Raught, B., Billia, F., Kannu, P., & Rottapel, R. (2020). Haploinsufficiency of RREB1 causes a Noonan-like RASopathy via epigenetic reprogramming of RAS-MAPK pathway genes. Nature Communications, 11(1), 4673. https://doi.org/10.1038/s41467-020-18483-9
10. Kramer, J., Roelofs, R. L., Wingbermühle, E., Pieters, S., Egger, J. (2025). Executive and social functioning in children and adolescents with Noonan syndromes: Cognition and behavior. Journal of the American Academy of Child and Adolescent Psychiatry (JAACAP Open). https://doi.org/10.1016/j.jaacop.2025.05.002
11. Leoni, C., Triumbari, E. K. A., Vollono, C., Onesimo, R., Podagrosi, M., Giorgio, V., Kuczynska, E., Veltri, S., Tartaglia, M., & Zampino, G. (2019). Pain in individuals with RASopathies: Prevalence and clinical characterization in a sample of 80 affected patients. American Journal of Medical Genetics Part A, 179(6), 940-947. https://doi.org/10.1002/ajmg.a.61111
12. Liao, J., & Mehta, L. (2019). Molecular Genetics of Noonan Syndrome and RASopathies. Pediatric Endocrinology Reviews, 16(2), 435-446. https://doi.org/10.17458/per.vol16.2019.lm.molecularnoonan
13. McNeill, A. M., Hudock, R. L., Foy, A. M. H., Shanley, R., Semrud-Clikeman, M., Pierpont, M. E., Berry, S. A., Sommer, K., Moertel, C. L., & Pierpont, E. I. (2019). Emotional functioning among children with neurofibromatosis type 1 or Noonan syndrome. American Journal of Medical Genetics Part A, 179(12), 2433-2446. https://doi.org/10.1002/ajmg.a.61361
14. Motta. M., Sagi-Dain, L., Krumbach, O. H. F., Hahn, A., Peleg, A., German, A., Lissewski, C., Coppola, S., Pantaleoni, F., Kocherscheid, L., Altmüller, F., Schanze, D., Logeswaran, T., Chahrokh-Zadeh, S., Munzig, A., Nakhaei-Rad, S., Cavé, H., Ahmadian, M. R., Tartaglia, M., & Zenker, M. (2020). Activating MRAS mutations cause Noonan syndrome associated with hypertrophic cardiomyopathy. Human Molecular Genetics, 29(11), 1772-1783. https://doi.org/10.1093/hmg/ddz108
15. Naylor, P. E., Bruno, J. L., Shrestha, S. B., Friedman, M., Jo, B., Reiss, A. L., & Green, T. (2023). Neuropsychiatric phenotypes in children with Noonan syndrome. Developmental medicine and child neurology, 65(11), 1520–1529. https://doi.org/10.1111/dmcn.15627

16. Noonan, J. A. (1968). Hypertelorism with Turner phenotype. A new syndrome with associated congenital heart disease. American Journal of Diseases of Children, 116(4), 373-380. https://doi.org/10.1001/archpedi.1968.02100020377005
17. Noonan, J. A. (2005). Noonan syndrome and related disorders. Progress in Pediatric Cardiology, 20(2), 177-185. https://doi.org/10.1016/j.ppedcard.2005.04.008
18. Noonan, J. A., & Ehmke, D. A. (1963). Associated non-cardiac malformations in children with congenital heart disease. Journal of Pediatrics, 63, 468-470.
19. Pierpont, E. I. (2016). Neuropsychological functioning in individuals with Noonan syndrome: A systematic literature review with educational and treatment recommendations. Journal of Pediatric Neuropsychology, 2, 14-33. https://doi.org/10.1007/s40817-015-0005-5
20. Pierpont, E. I., Hudock, R. L., Foy, A. M., Semrud-Clikeman, M., Pierpont, M. E., Berry, S. A., Shanley, R., Rubin, N., Sommer, K., & Moertel, C. L. (2018). Social skills in children with RASopathies: A comparison of Noonan syndrome and neurofibromatosis type 1. Journal of Neurodevelopmental Disorders, 10, 21. https://doi.org/10.1186/s11689-018-9239-8
21. Roberts, A. E., Allanson, J. E., Tartaglia, M., & Gelb, B. D. (2013). Noonan syndrome. The Lancet, 381(9863), 333-342. https://doi.org/10.1016/S0140-6736(12)61023-X
22. Roelofs, R. L., Wingbermühle, E., van der Heijden, P. T., Jonkers, R., de Haan, M., Kessels, R. P. C., & Egger, J. I. M. (2019). Personality and psychopathology in adults with Noonan syndrome. Journal of Clinical Psychology in Medical Settings, 27, 256-267. https://doi.org/10.1007/s10880-019-09659-7
23. Tajan, M., Paccoud, R., Branka, S., Edouard, T., & Yart, A. (2018). The RASopathy family: Consequences of germline activation of the RAS/MAPK pathway. Endocrine Reviews, 39(5), 676-700. https://doi.org/10.1210/er.2017-00232
24. Tartaglia, M., Aoki, Y., & Gelb, B. D. (2022). The molecular genetics of RASopathies: An update on novel disease genes and new disorders. American Journal of Medical Genetics Part C: Seminars in Medical Genetics, 190C, 425-439. https://doi.org/10.1002/ajmg.c.32012
25. Tartaglia, M., Gelb, B. D., & Zenker, M. (2011). Noonan syndrome and clinically related disorders. Best Practice and Research: Clinical Endocrinology and Metabolism, 25(1), 161-179. https://doi.org/10.1016/j.beem.2010.09.002
26. Van der Burgt, I., Berends, E., Lommen, E., van Beersum, S., Hamel, B., &
27. Mariman, E. (1994). Clinical and molecular studies in a large Dutch family with Noonan syndrome. American Journal of Medical Genetics, 53(2), 187-191. https://doi.org/10.1002/ajmg.1320530213
28. Wingbermühle, E., Egger, J. I. M., Verhoeven, W. M. A., van der Burgt, I., & Kessels, R. P. C. (2012a). Affective functioning and social cognition in Noonan syndrome. Psychological Medicine, 42(2), 419-426. https://doi.org/10.1017/S0033291711001115
29. Wingbermühle, E., Roelofs, R. L., van der Burgt, I., Souren, P. M., Verhoeven,W. M. A., Kessels, R. P. C., & Egger, J. I. M. (2012b). Cognitive functioning of adults with Noonan syndrome: A case-control study. Genes, Brain & Behavior, 11(7), 785-793. https://doi.org/10.1111/j.1601-183X.2012.00821.x
30. Wingbermühle, E., Roelofs, R. L., Oomens, W., Kramer, J., Draaisma, J. M. T., Leenders, E., Kleefstra, T., Kessels, R. P. C., Egger, J. I. M. (2022). Cognitive Phenotype and Psychopathology in Noonan Syndrome Spectrum Disorders through Various Ras/MAPK Pathway Associated Gene Variants. Journal of Clinical Medicine, 11, 4735. https://doi.org/10.3390/jcm11164735
31. Zenker, M. (2022). Clinical overview on RASopathies. American Journal of Medical Genetics Part C: Seminars in Medical Genetics, 190C, 414-424. https://doi.org/10.1002/ajmg.c.32015

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