7TH INTERNATIONAL RASOPATHIES SYMPOSIUM

Arrixaca
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Clinical and molecular characterization of a group of Spanish and German patients with Noonan syndrome

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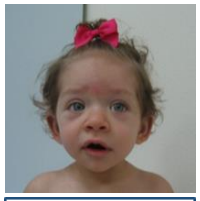
INTRODUCTION

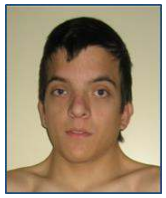
RASopathies are a group of diseases due to variants in genes that encode components or regulators of the RAS/MAPK pathway. Noonan syndrome (NS) is the most common of them, with an estimated prevalence of 1:2,500 live newborns *(Nora et al. 1974).* Its clinical manifestations include: distinctive craniofacial features, heart defects, short stature, intellectual disability (ID) and increased tumor risk, among others *(Noonan 1994)*


PTPN11


SOS1


RAF1


RIT1


KRAS


NRAS


CBL

OBJECTIVES

- Clinical and molecular characterization of patients from Murcia (Spain) and Essen (Germany) with NS, and comparison with published series
- Estimation of its prevalence in Murcia
- Study of the reasons for referral to Medical Genetics and the referral units
- Identification of unusual features
- Study of the craniofacial phenotype and its correlation with the severity of the multisystem involvement
- Genotype-phenotype correlation analysis
- Review of complementary examinations and comparison with those recommended in the clinical follow-up guidelines

MATERIAL AND METHODS

- Observational, descriptive, retrospective and international collaborative study
- Target population: patients with a molecularly confirmed diagnosis of NS from:
  - -Medical Genetics Section, Hospital Clínico Univeristario Virgen de la Arrixaca, Murcia, Spain
  - -Institute of Human Genetics, Universitätsklinikum, Essen, Germany
- Study period: Essen: 1994-2012 / Murcia: 2002-2018
- Review of medical records and collection of clinical and molecular data, including, among others, all variables in the questionnaire of the "European network on Noonan syndrome and related disorders" (NsEuroNet) (https://nseuronet.com)
- Analysis of the photographs with the facial recognition program by Face2gene (http://suite.face2gene.com)

DAAD
Deutscher Akademischer Austauschdienst

RESULTS

88 CASES

Mean age at referral: 5.79 ± 7.60 years (R: 1 month to 36 years).

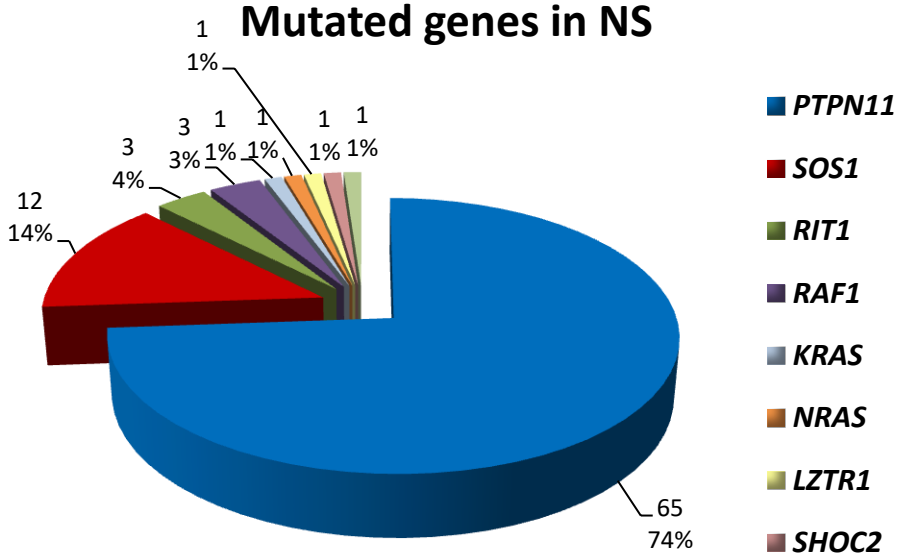
54.6% females / 45.4% males

Main reasons for referral: dysmorphia 79.6%, heart defects 42% and short stature 25%

Main referral units: General Pediatrics 29% and Pediatric Cardiology 23%

Prevalence of NS in Murcia: 1/7348 RNV

Mutated genes in NS



66.7% *de novo*

Clinical findings:

- Heart defects: 76% (PVS 52.4%, 24.4% HCM)

  *HCM: PTPN11 (21.3%) vs RAF1 (100%) (**p=0.002**)*
- Short stature: 53%

  *PTPN11 (60%) vs SOS1 (27.3%) (**p=0.04**)*
- Microcephaly: 40%

  *PTPN11 (49%) vs SOS1 (11%) (**p=0.03**)*
- ID: 35%
- Lymphatic anomalies: 22.7%
- Kidney anomalies: 22.6%
- JMML: 4.2%

Unusual features: Hernias: 14/29 (48.3%); Syndactyly: 14/36 (39%); Dystrophic nails: 13/34 (38.2%); Single palmar crease: 7/22 (31.8%); Hemangiomas: 10/61 (16.4%); Body asymmetry: 3/27 (11%); Anteriorly placed anus: 4/69 (5.8%)

Face2Gene (n=58)	
Typical (high compatibility)	33 (57%)
Ranking NS first diagnosis	55 (94.8%)

Van der Burgt criteria		
Typical face	**Suggestive face**	**Atypical face**
33/33 (100%)	16/17 (94%)	6/8 (75%)
Typical vs atypical (**p=0.003**)		

	Severe phenotype*	Mild phenotype	*p*
ID	5/8 (62.5%)	8/32 (25%)	0.07

*Combination of typical craniofacial features (high in Face2Gene), heart defect, short stature and thorax deformity

NEURODEVELOPMENT

	Motor delay	Normal motor development	*P*
Hypotonia	13/14 (93%)	10/21 (47.6%)	**0.01**
ID	9/16 (56.3%)	5/33 (15.2%)	**0.006**

	ID	Normal intelligence	*p*
Heart surgery	8/13 (61.5%)	6/27 (22.2%)	**0.015**
Low weight	9/18 (50%)	5/39 (12.8%)	**0.006**
Short stature	16/19 (84.2%)	16/41 (39%)	**0.002**

	Microcephaly	Normal OFC	*p*
Behavioural disorder	11/19 (58%)	8/32 (25%)	**0.035**
ID	12/21 (57%)	5/30 (16.7%)	**0.006**

	CNS anomalies	Normal neuroimaging	p
Seizures	7/20 (35%)	1/25 (4%)	**0.015**

CONCLUSIONS

- We present a wide series of NS cases with clinical manifestations, mostly, in accordance with previous publications
- There is a large prevalence of microcephaly, higher in PTPN11, associated with ID and behavioral alteration, not previously reported
- There appears to be greater severity of systemic involvement accompanying the severity of the craniofacial phenotype
- Although without reaching statistical significance, patients with more severe manifestations of the disease seem to associate ID more frequently
- CNS abnormalities are associated with the presence of seizures and are close regarding ID
- As for the unusual clinical features, the presence of anteriorly placed anus and hemihypertrophy are described for the first time. It is worth noting the presence, in a considerable percentage, of syndactyly, hernias and single palmar crease, in which we describe a higher prevalence than that of the general population
- The mutational distribution in the series is similar to that reported in the literature, with a higher percentage of pathogenic variants in *PTPN11*, probably due to the greater accessibility to its study and its correlation with a more classic phenotype
- The estimated prevalence of NS in Murcia is lower than previously reported, the development of strategies to improve its detection being necessary
- Greater awareness of adult specialties towards this disease is necessary

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