

Introduction

- Noonan syndrome (NS), which occurs in approximately 1:1000–1:2500 individuals, is characterized by variable presentation of a wide range of phenotypes, including short stature, congenital heart defects, distinctive facial features, skeletal defects, a broad or webbed neck, coagulation deficiencies, and mild cognitive impairment.
- Individuals with NS also have an increased risk of developing various types of cancer, often with early onset.
- Because of ascertainment bias and variable expressivity often with subtle features, many affected adults are diagnosed only after the birth of a more noticeably affected infant.

Case report

Clinical features

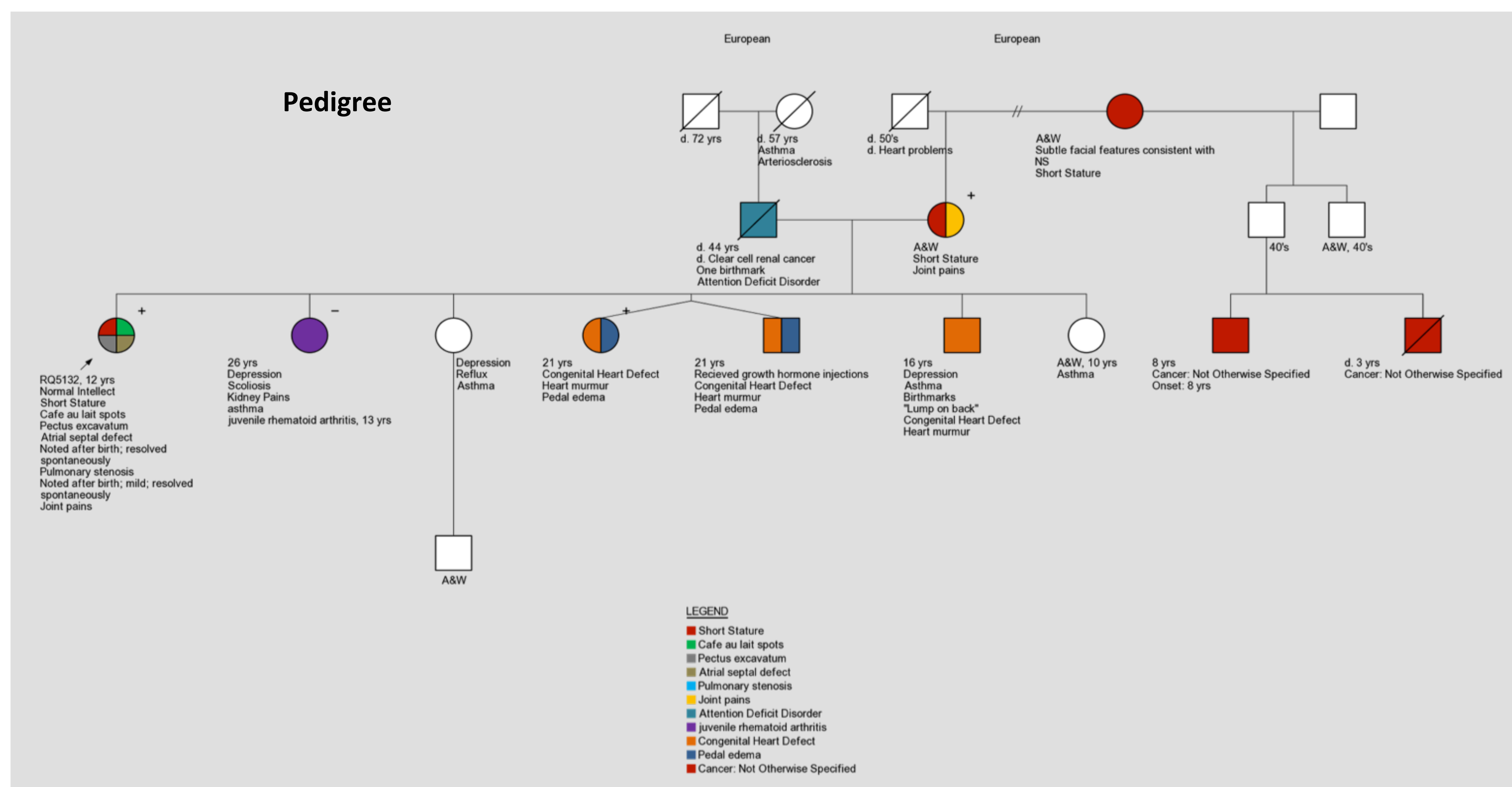
- The proband is a 12-year-old female of normal intellect with short stature, pectus excavatum, café au lait spots, and joint pain.
- Proband also has a history of atrial septal defect and mild pulmonary stenosis noted shortly after birth that resolved spontaneously.
- She is one of seven children born to her mother and father.

Molecular testing

- Next-generation sequencing of 12 genes (Noonan full panel with deletion/duplication analysis, Invitae, San Francisco, CA) identified a missense variant in exon 3 of the *PTPN11* gene: c.209A>G (p.Lys70Arg) and is classified as likely pathogenic.
 - Highly conserved lysine residue at codon 70 of the PTPN11 protein is replaced with an arginine residue. There is a small physicochemical difference between these two amino acids.
 - This variant has not been published as a disease-associated variant in the literature and has not been reported as a benign polymorphism in population databases. However, variant has been observed in five affected individuals and segregates with features of Noonan syndrome in one family (ClinVar: RCV000037634).
 - Algorithms developed to predict the effect of missense changes on protein structure and function do not agree on the potential impact of this variant (SIFT: “deleterious;” PolyPhen-2: “possibly damaging;” Align-GVGD: “Class C0.”)
 - This variant is located within a functionally conserved N-SH2 domain and a significant number of previously reported PTPN11 pathogenic variants have been found within this domain (PMID: 16377799).

Family testing

- Testing of the mother revealed that the PTPN11 variant was maternally inherited.
- Subsequently, analysis of the PTPN11 gene was performed on two of the proband’s siblings. Siblings’ results are denoted as negative (-) or positive (+) for the familial PTPN11 variant in the pedigree.
- The familial PTPN11 variant was observed in the proband, her mother, and 21-year-old sister. A third relative is expected to be sent for PTPN11 gene analysis.



Discussion

- Noonan syndrome is a pediatric developmental disorder, categorized as a RASopathy, that is multisystemic with variable expressivity. Testing large families with detailed clinical findings provides valuable information in understanding the similarities and differences of phenotypic characteristics in family members with the same pathogenic variant.
- In this family study, the mother and maternal grandmother of the proband are generally healthy but both have short stature. The grandmother also appears to have subtle facial features of NS. Three of six proband siblings have heart murmurs, and one of these individuals also has mild learning difficulties and cafe au lait macules. Other obvious features of NS were not noted for these individuals. Notably, two maternal half cousins of the proband had histories of childhood cancers.
- Among the three family members (proband, mother, 21-year-old sister) that have tested positive for the likely pathogenic PTPN11 variant, there did not appear to be a phenotype that was completely concordant in the individuals. Short stature and joint pains are noted in the proband and her mother while the proband and sister had a history of congenital heart defects.
- The 26-year-old sister tested negative for the PTPN11 likely pathogenic variant, and did not have short stature or congenital heart defects described in affected family members.
- Testing the grandmother, who appears to have features consistent with NS, could potentially establish vertical transmission across three generations. In addition, testing of the two maternal half cousins could be informative since NS is associated with an increased risk for childhood cancers.

Conclusion

- The findings in this report illustrate the importance of testing families with variable expressivity to expand the clinical and molecular spectrums of Noonan syndrome.

References

- GeneReviews®[Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015. 2001 Nov 15 [updated 2011 Aug 04].
- Kontaridis MI et al., (2006) *J Biol Chem.* 10;281(10): 6785-6792.