

Paternal germline origin and sex-ratio distortion in transmission of *PTPN11* mutations in Noonan syndrome

Marco Tartaglia *et al*

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Introduction

Noonan syndrome (NS) is a developmental disorder characterised by short stature, facial dysmorphism, skeletal, hematologic and congenital heart defects. Prevalence is thought to be 1 in 1000-2500 live births making it the most common non-chromosomal syndrome with cardiac involvement.

NS is an autosomal dominant condition. A significant number of cases appear to arise from *de novo* mutations. *PTPN11* mutations represent a major cause and appear to be more prevalent among families segregating NS than sporadic cases.

Issue addressed in paper

This paper investigated three main issues:

1. The parental origin of *de novo* *PTPN11* lesions. The intronic portions flanking exonic *PTPN11* lesions were analysed for the presence of polymorphic sites in 49 cases of sporadic NS. In each case the affected individual was heterozygous for a confirmed *de novo* *PTPN11* mutation in exon 3 or 8 and had unaffected parents.
2. The effect of paternal age in NS. The age of fathers among separate cohorts of NS probands with and without *PTPN11* mutations was compared with population data.
3. The evidence for a sex-ratio bias in transmission of sporadic *PTPN11* lesions.

Summary of Findings

1. A heterogeneous condition for intronic polymorphisms was identified in 15 individuals and parental origin of mutation was identified in 14 cases. **All mutations were paternally inherited.**
2. **Advanced paternal age was observed among both cohorts.** The average age of fathers in the *PTPN11* related group was 6.1y older than the population average and 4y older in the *PTPN11* negative group.
3. A significant sex-ratio bias was observed favouring transmission to males in subjects with sporadic NS caused by *PTPN11* mutations – 66 males to 31 females. Families inheriting NS with *PTPN11* mutations were further analysed to see if the bias was still present with the founder individual excluded. In this case NS was transmitted to 37 males versus 21 females.

Conclusions

This paper provides the first documented evidence for paternal origin of *de novo* *PTPN11* mutations in NS.

There is also evidence for an association with advanced paternal age and a significant sex-ratio bias favouring transmission to males.

The paper went on to discuss the following points:

- Results confirmed previous studies supporting the predominance of paternal origin of point mutations in the majority of autosomal dominant diseases.
- This phenomenon of paternal origin of sporadic mutations is not widely understood.
- One possible explanation is that gain of function mutations (such as a *PTPN11* mutation) could result in selective advantage in sperm motility and capacitation.
- The distorted male: female sex ratio could be due to sex specific developmental effects, this is supported by the fact that fetal lethality has been reported in the disorder.