Case Report / Case Study

# Nager Syndrome Co-Harboring Mutation Consistent with Stickler Syndrome: A Rare Case Report


## Abstract

Nager syndrome, or preaxial acrofacial dysostosis, is a rare malformation characterized by abnormalities of the craniofacial skeleton and limbs. Although most cases are sporadic and some cases have been demonstrated to have an autosomal dominant or recessive mode of inheritance, SF3B4 haploinsufficiency is the most common genetic abnormality identified in this, of which only around 100 cases have been reported so far in the literature. Classically characterized by ante-mongoloid slant, retrognathia, midface retrusion and proximal limb abnormalities like thumb aplasia or hypoplasia, arachnodactyly and radioulnar synostosis, the significant morbidity and mortality in this challenging condition is primarily due to airway abnormalities causing respiratory obstruction. We report a case of genetically confirmed Nager syndrome simultaneously harbouring a mutation consistent with Stickler syndrome type II.


## Introduction

Nager syndrome, or preaxial acrofacial dysostosis, is a sporadic malformation syndrome first reported by Nager and de Reynier in 1948. Around 100 cases have been reported so far in literature, few of them have been genetically confirmed [1]. Severe oromandibular hypogenesis and upper limb defects with relative sparing of the lower limbs are characteristic of this illness. A tenuous airway prone to severe respiratory obstruction, necessitating tracheostomy tube placement by the end of infancy, is the primary cause of morbidity and mortality in this disorder [2]. We report a neonate born in our institute with gross dysmorphic features, later was proven genetically as a case of Nager Acrofacial Dysostosis, also harbouring another mutation consistent with Stickler syndrome.

## Case Presentation

The prepositus is a first order neonate who was born in our institute by caesarean section and was referred to the paediatrics department for evaluation of gross craniofacial and limb anomalies. He was delivered at term with a birth weight of 2290 g (<3$^{rd}$ centile), with a length of 48 cm and a head circumference of 33 cm. The morphologic examination of the neonate revealed up-slanting palpebral fissures, malar hypoplasia and severe micrognathia with cleft palate. (**Figure 1**)

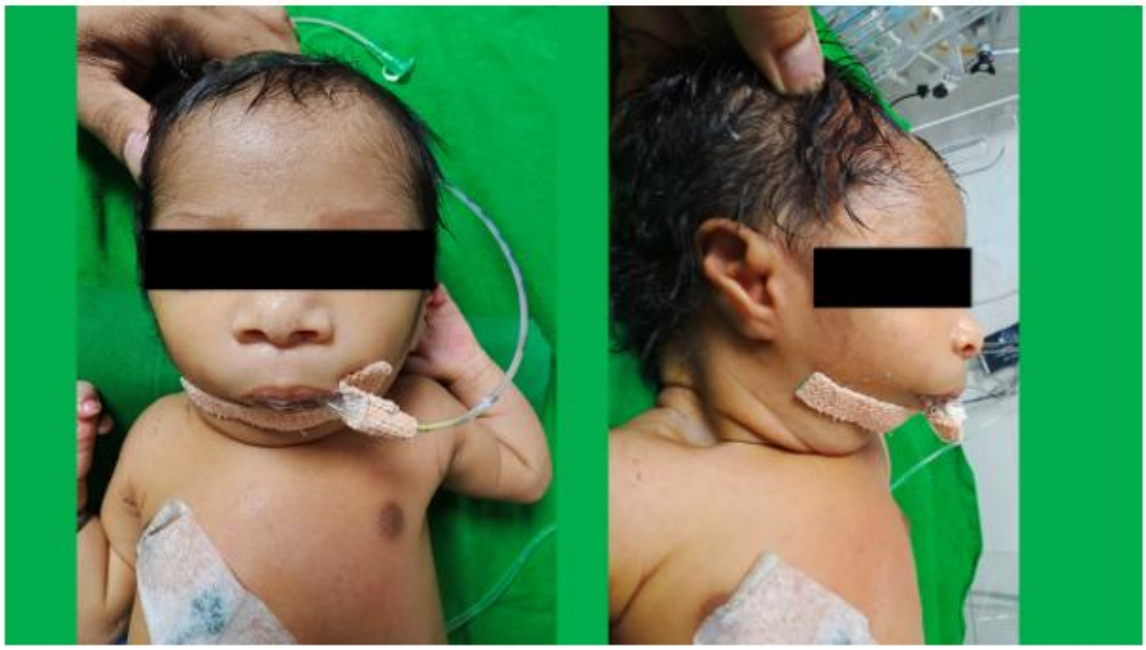

*Figure 1: Frontal and Lateral facial profile of the patient showing severe retrognathia*

There was right thumb aplasia (type 5) and type 2 thumb hypoplasia on left side with hypoplastic thenar muscles (Blauth classification) [3]. (**Figure 2**)

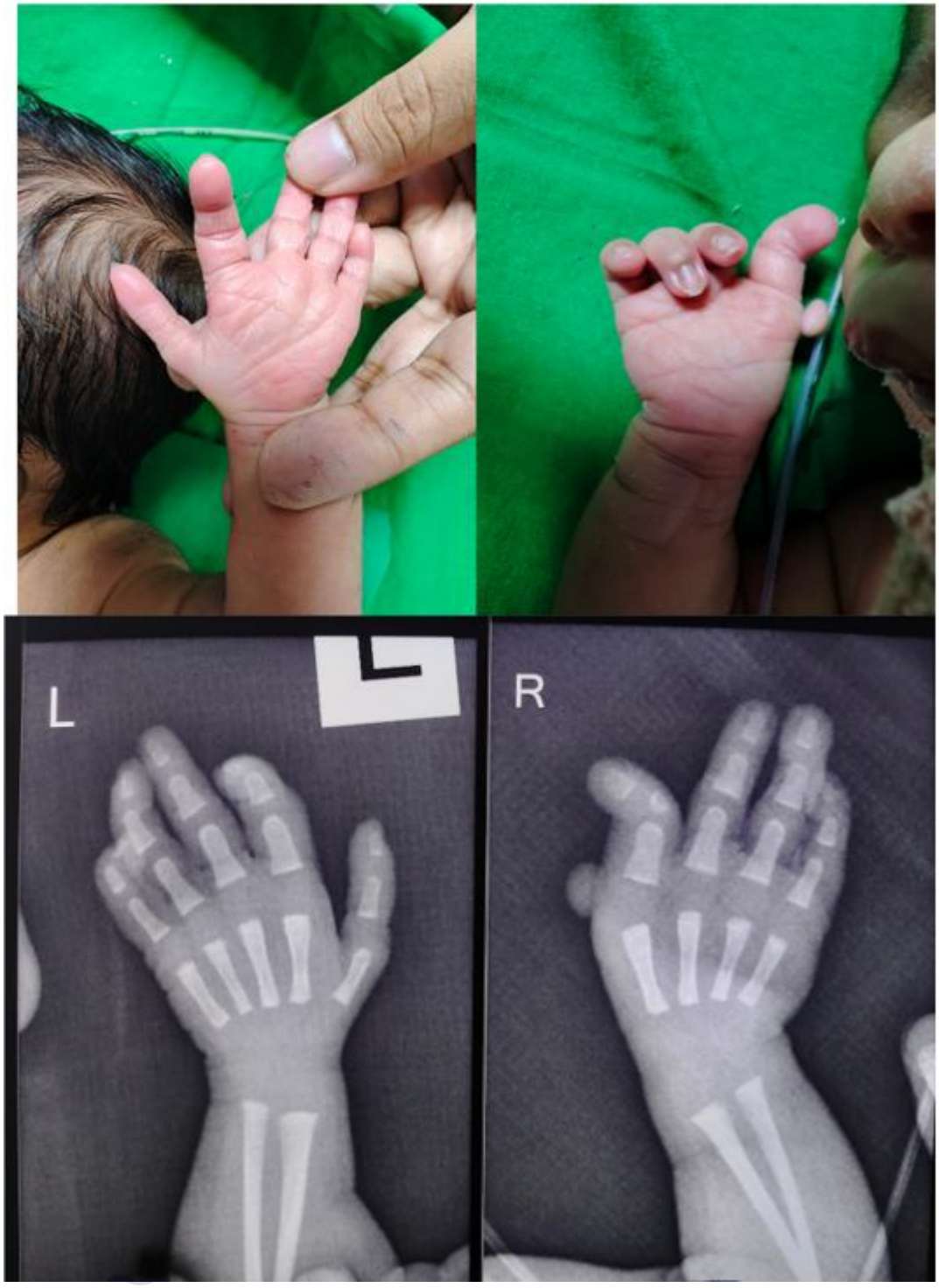


*Figure 2: Gross appearance and x-rays of hands showing Thumb Hypoplasia (Left) and Thumb Aplasia (Right)*

There was no gross abnormality in bilateral lower limbs and no ocular abnormalities. There was no similar history in any other family members, and there was no history of previous pregnancy loss or sibling death either. Echocardiography was normal. There were no ocular abnormalities and the fundus examination revealed no significant abnormalities. Based upon the morphologic findings, various differential diagnoses of Pierre Robin Sequence, Nager Syndrome, Miller syndrome and Stickler syndrome were considered, and Whole Exome Sequencing (WES) was performed after obtaining consent from parents. A heterozygous

frameshift variant c.956dupT in Exon 5 of the *SF3B4* gene that results in the amino acid substitution p.Leu319fs*108 was identified, confirming a diagnosis of Nager syndrome with an autosomal dominant inheritance. Another heterozygous missense variant c.4307C>T in Exon 58 of the *COL11A1* gene that results in the amino acid substitution p.Pro1436Leu was also identified associated with Stickler Syndrome type II. Feeding was established after placing of an orogastric tube with airway protective measures. After proper counselling regarding the prognosis and what the future holds for the baby, he was discharged and parents were advised to consult a plastic surgeon for reconstructive surgery of the child, such as pollicization of the index finger. The parents were advised for regular follow-up of the baby with regular change of the orogastric tube by a paediatrician. On follow-up visit at the end of the second month of life, the baby was doing well and gaining adequate weight while being on orogastric tube feeding, and the parents had been advised to proceed for surgery after completion of nine months of age by the plastic surgeon.

## Discussion

Nager syndrome is the prototype of a group of rare disorders collectively known as Acrofacial Dysostosis (AFD), characterized by malformations of the craniofacial skeleton and limbs. It is a rare congenital malformation syndrome resulting from abnormal development of first and second branchial arches and limb buds [4]. First reported by Slingenberg in 1908 and recognized by Nager and de Reynier in 1948, the exact cause of this abnormal development is still needs to be completed [5]. Although the majority of the cases are sporadic, the mode of inheritance can be either Autosomal Dominant or Autosomal Recessive and multiple families showing highly variable expressivity of the disease have been reported [4,6].

Appropriate genetic expression in eukaryotic cells relies upon pre-mRNA splicing, an important step in which precise removal of introns from pre-mRNA gives rise to mature mRNA. This splicing takes place in Spliceosomes, large RNA-protein complexes, that consist of a set of snRNPs, including U1, U2, U4/U6 and U5 complexes. SF3B4, the only gene associated with Nager acrofacial dysostosis, encodes a core subunit of the metazoan SF3b complex, part of the U2-type spliceosome [7]. It is also an important gene related to the Bone Morphogenic Protein (BMP) signalling pathway [8]. Haploinsufficiency of SF3B4 is found in greater than 50% of cases of Nager syndrome [6]. Extensive genetic heterogeneity is suggested by the identification of deletions encompassing SF3B4 in some cases, which has been helpful in prenatal diagnosis of fetuses as early as 12 weeks of gestation by virtue of chromosomal microarray [9]. The patients bearing frameshift SF3B4 variants have been reported to have more severe clinical manifestations, while variants in exons 2 and 3 often demonstrate higher incidence of cardiac malformations [10].

Distinguished from Mandibulofacial dysostosis, Nager syndrome affects the muscles and nerves associated with mastication, the lower jaw, bones of the middle ear and the muscles of facial expression [4]. The major clinical features of this disorder include down-slanting palpebral fissures, micrognathia, malar hypoplasia, pre-axial limb abnormalities such as small or absent thumbs, triphalangeal thumbs, arachnodactyly, radial aplasia or hypoplasia and radio-ulnar synostosis [6,11]. Although congenital cardiac defects like septal defects and tetralogy of Fallot have been reported, they are extremely uncommon [2].

The major problem faced by parents in the neonatal period and infancy is feeding issues courtesy of cleft palate and retrognathia, often necessitating the placement of a feeding tube into the stomach. Trismus and glossoptosis as a consequence of mandibular abnormalities can lead to life threatening respiratory distress in infancy, entailing placement of a tracheostomy tube [11,12]. Later on, Conductive Hearing Loss (CHL) and speech delay further complicate the development of the children affected with this syndrome [13]. Patients surviving into adulthood are typically riddled with a history of multiple interventions such as repair of cleft palate, chin implant, bone-anchored hearing aid implantation, spinal fusion and extremely difficult intubation when required [12]. If untreated, cases have been reported where CHL has gradually progressed to Sensorineural Hearing Loss (SNHL), culminating in mixed hearing loss, not amenable to surgical interventions [13]. There have been case reports of patients presenting as late as 14-years of age for the first time, for surgical correction of microtia-anotia, who have later been confirmed to be a case of Nager Syndrome [14].

## Conclusion

A multidisciplinary team consisting of neonatologists, otorhinolaryngologists, anesthesiologists, obstetricians, audiologists, plastic surgeons, and geneticists is best suited to care for babies afflicted with this rare and challenging disorder, for which a high index of suspicion and availability of genetic tests like whole exome sequencing or chromosomal microarray analysis can prove helpful in prenatal or early neonatal diagnosis. Pediatric intensivists need to be highly skillful in managing conditions with difficult airways such as this and must always be prepared for emergency and elective tracheostomy. The availability of equipment like pediatric video laryngoscope and fibre optic bronchoscope can aid in managing patients with Nager syndrome.

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