

# **Haploinsufficiency of SF3B2 Causes Craniofacial Microsomia**

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## **BACKGROUND**

Craniofacial microsomia (CFM) is the second most common congenital facial anomaly, yet its genetic etiology remains largely unexplored.

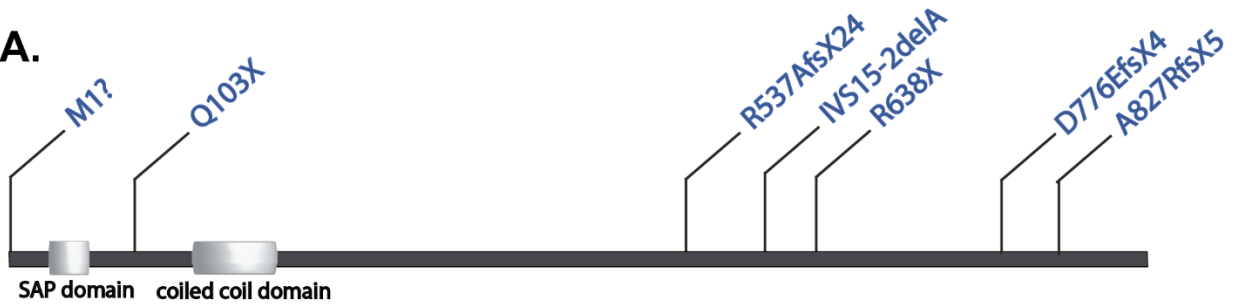
## **METHODS**

We performed whole-exome or genome sequencing of 146 kindreds with sporadic (n=138) or familial (n=8) CFM. The burden of de novo and transmitted alleles in each gene was studied in probands.

## **CONCLUSIONS**

We identified a highly significant burden of loss of function variants in SF3B2 ( $P=3.8 \times 10^{-10}$ ), a component of the U2 small nuclear ribonucleoprotein complex, in probands. We describe twenty individuals from seven kindreds harboring de novo or transmitted haploinsufficient variants in SF3B2. Probands presented with mandibular hypoplasia, microtia, facial and preauricular tags, epibulbar dermoids, lateral oral clefts in addition to skeletal and cardiac abnormalities. Targeted morpholino knockdown of SF3B2 in *Xenopus* resulted in disruption of cranial neural crest precursor formation and subsequent craniofacial cartilage defects, supporting a link between spliceosomal dysfunction and impaired neural crest development in congenital craniofacial disease. The results establish haploinsufficient variants in SF3B2 as the most prevalent genetic cause of CFM, explaining ~3% of sporadic and ~25% of familial cases.

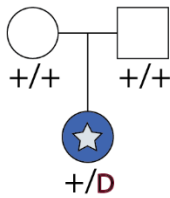
**A.**



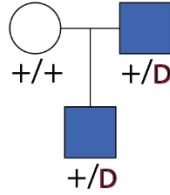
**B.**

- CRANIOFACIAL MICROSOMIA
- ☆ DE NOVO MUTATION

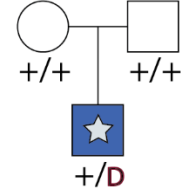
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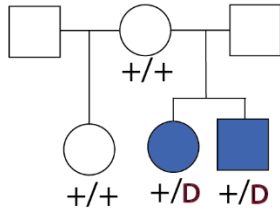
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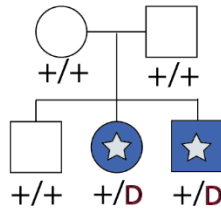
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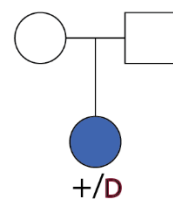
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**KINDRED 5**  
c.C1912T:p.**R638X**



**KINDRED 6**  
c.C307T:p.**Q103X**



**KINDRED 7**  
c.A1T:p.**M1?**

