

Identification of mutations in CUL7 in 3M syndrome

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Introduction

Intrauterine growth retardation is caused by maternal, fetal or placental factors that result in impaired endovascular trophoblast invasion and reduced placental perfusion. Most cases are unexplained. 3-M syndrome is an autosomal recessive disorder characterised by intrauterine growth retardation alongside facial dysmorphism, large head circumference and normal intelligence and endocrine function.

Issue addressed in paper

From DNA analysis of 29 families with 3M syndrome the underlying gene was mapped to chromosome 6p21.1. Cullin 7 (CUL7) is present in this region. It was considered a good candidate gene because of data from the *Cul7* mouse model.

Summary of findings

Direct sequencing of CUL7 was carried out in individuals with 3M syndrome. 25 distinct mutations were found – 19 predicted premature terminations of translation and 6 missense mutations. Northern blot and RT-PCR analysis supported the conclusion that CUL7 RNA is expressed in at least a subset of individuals with 3-M syndrome.

CUL7 is believed to have a scaffold role in assembling an E3 ubiquitin ligase complex that targets proteins for ubiquitination and subsequent degradation. The E3 ubiquitin ligase complex contains SKp1, Fbx29 and ROC1. CUL7 interacts with the Skp1-Fbx29 heterodimer and the ROC1 RING finger protein, which then recruits E2-conjugating enzyme.

The predominance of null mutations found suggests that 3-M syndrome may be caused by loss of ability of CUL7 to assemble the E3 ligase complex.

Approximately 50% of 3-M causing mutations were located in the cullin domain which is crucial for binding ROC1. The molecular defects caused by the CUL7 nonsense and missense mutations R1445X and H1464P were studied further. Both mutations were shown to disrupt the ability of CUL7 to interact with ROC1, which is a crucial step for the assembly of polyubiquitin chains.

Conclusion

This study provides the first evidence to implicate cullin gene mutations in a human disease. Because 3-M syndrome is characterised by intrauterine growth retardation, authors speculate that factors involved in human fetoplacental vasculogenesis or angiogenesis might be putative targets for the CUL7 E3 ligase complex. Further investigation into the specific role of the CUL-7 dependant pathway is required.