

Tall stature and macrodactyly of the great toes due to a novel variant in the natriuretic peptide receptor 2 gene

Session Growth and Syndromes 2

Introduction

Mutations in the natriuretic peptide receptor 2 gene (NPR2) are responsible for monogenic growth disorders¹⁻³. NPR2 catalyses the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) which in growth plate chondrocytes fosters hypertrophy, differentiation and extracellular matrix deposition leading to longitudinal bone growth.

We describe a novel gain-of-function variant in a family with tall stature and macrodactyly of the great toes.

Conclusion

In vitro assays with variant NPR2 transfected HEK 293 cells demonstrated:

- reduced NPR2 expression levels in light of;
- a markedly enhanced ligand-independent cGMP production and greater responsiveness to CNP.

Future research will focus on building 3D models of the transmembrane segment to explain these findings.

Patients

Mother (188.1 cm; +2.77 SDS):

- high dose estrogen treatment during adolescence to reduce adult height
- long great toes
- bilateral percutaneous epiphysiodesis of great toes twice

6 year old daughter (132.6 cm; +1.96 SDS) and

4 year old daughter (110.2 cm; +1.30 SDS):

- long great toes (Figure 1), ankle valgus and positive thumb sign
- diminished span to height ratio due to shortened forearms (mesomelia)

Father's height is 178 cm (-0.58 SDS); target height is 175 cm (+0.68 SDS).

Skeletal surveys:

- pseudo-epiphyses of the mid- and proximal phalanges of all fingers and both great toes (Figures 1 and 2)



Figure 1: Feet of eldest daughter (upper row) and youngest daughter (lower row)

Figure 2: X-ray of eldest daughter. The red square shows a pseudo-epiphysis

Results

Genotype - Novel heterozygous NPR2 variant c.1444_1449delATGCTG p.Met482_Leu483del

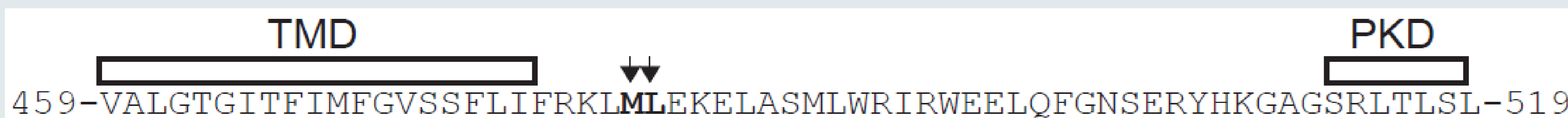


Figure 3: Amino acids 459-519; black arrows are the deleted amino acids
TMD: transmembrane domain
PKD: protein kinase domain

Functional assays - HEK 293 cells were transfected with mutant NPR2 by site-directed mutagenesis

Figure 4: Western blot analysis

of NPR2 expression levels in HEK 293 cells

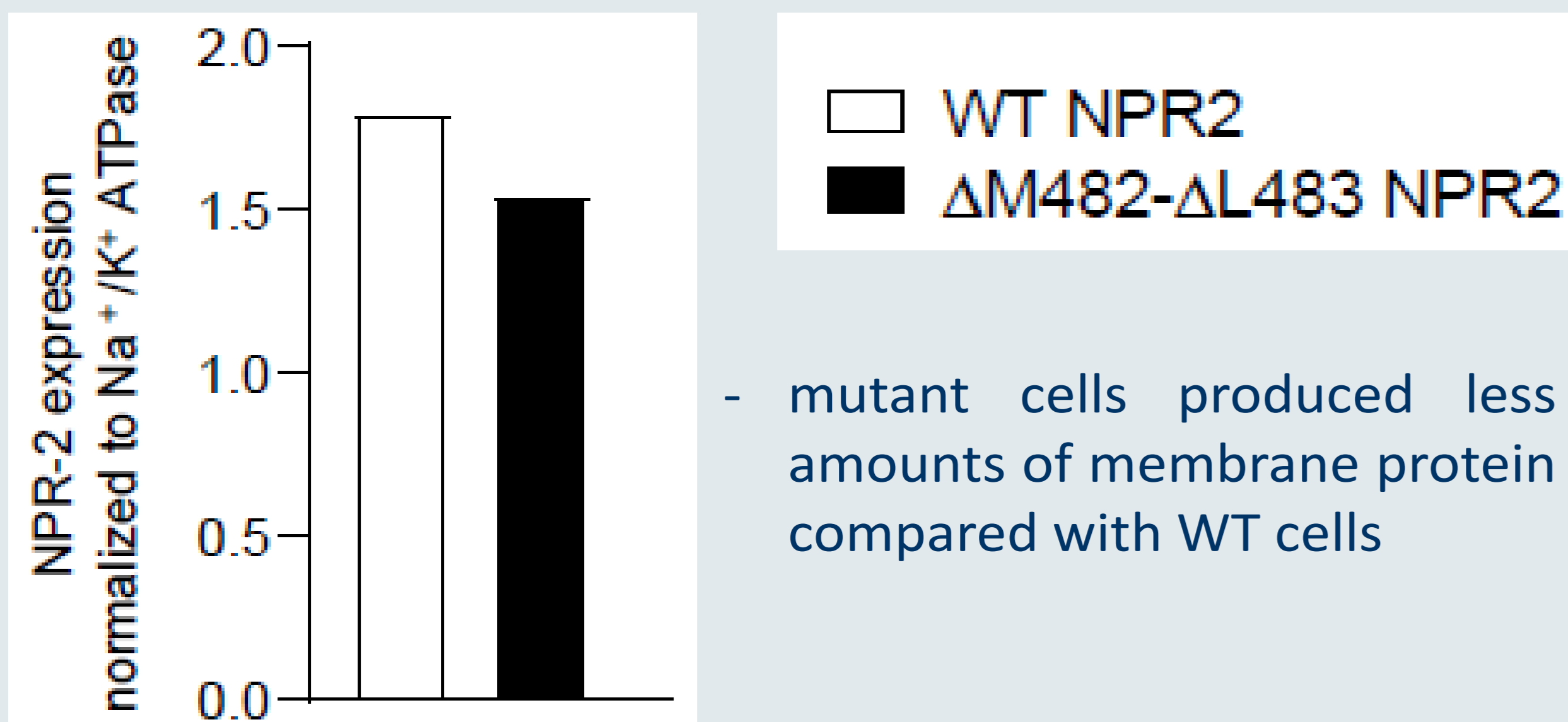
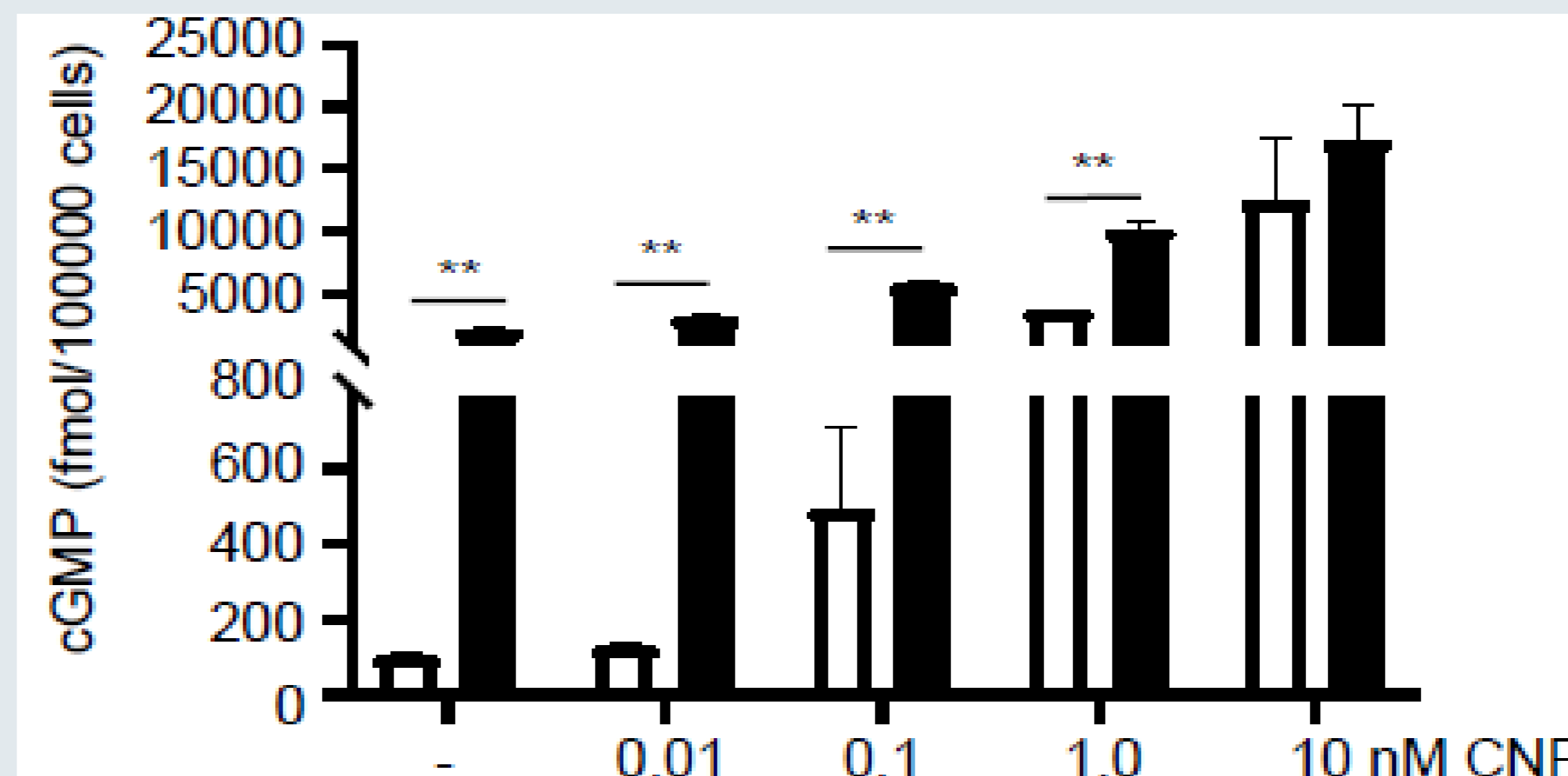


Figure 5: HEK 293 cell cGMP levels

and response to CNP, **P<0.01 vs control



- responses to low, physiological CNP concentrations were augmented
- responses to higher CNP concentrations (10 and 100nM) were comparable with WT NPR2
- the diminished effect of high CNP concentrations on cGMP levels is probably due to the attenuated expression

References: 1. Miura K, et al. PLoS One. 2012;7(8):e42180. 2. Hannema SE, et al. JCEM. 2013;98(12):E1988-98. 3. Miura K, et al. Am J Med Genet A. 2014;164A(1):156-63.

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