C03.4 Expanding genotype-phenotype associations in biglycan-related Meester-Loeys syndrome

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Loss-of-function variants in *BGN*, an X-linked gene coding for biglycan, are associated with Meester-Loeys syndrome (MRLS), a syndromic form of aortic aneurysm/dissection. Since the initial publication of five families in 2017, we identified eleven additional MRLS families. All sixteen probands, except two, are male and had an average age at presentation of 38 years. Thirteen males and one female presented with aortic ($n = 10$) and/or arterial ($n = 6$) aneurysms/dissections, one male (11y) presented with syndromic features without cardiovascular symptoms (yet), and one female proband (42y) was identified as part of comprehensive prenatal testing. An additional 33 *BGN* variant-harbouring family members (M/F:6/27) were identified with cascade screening. Their phenotype ranged from no cardiovascular or connective tissue phenotype to death due to aortic dissection. Identified *BGN* mutations causing a stop codon insertion, frameshift, or splicing defect and partial *BGN* deletions were shown to result in loss-of-function by cDNA and Western Blot analysis of skin fibroblasts of seven probands, or were strongly predicted to lead to loss-of-function based on the nature of the variant. Interestingly, a male proband with a deletion encompassing exon 2–8 of *BGN* presented with a more severe skeletal phenotype. RNA sequencing revealed expressional activation of a downstream ATPase (*ATP2B3*; normally repressed in skin fibroblasts) driven by the remnant *BGN* promotor as a possible explanation. These observations indicate that extensive analysis at RNA, cDNA and protein level is required before concluding on the pathogenicity of *BGN* variants; and distinct mutational mechanisms may underlie the wide phenotypic spectrum of MRLS patients.

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C03.5 Rare heterozygous variants in PTCH1 are associated with bladder exstrophy-epispadias complex

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Bladder exstrophy-epispadias complex (BEEC) is a clinically and genetically heterogeneous devastating developmental disorder which presents at birth in its classic form with a bladder exposed through the abdominal wall. Most affected children have no family history and it usually occurs as an isolated developmental anomaly. A small number of affected children have duplications at chromosome 22q11.

Through exome and Sanger sequencing, we identified 9 of 277 individuals with BEEC with very rare (MAF $<2 \times 10^{-5}$) heterozygous variants in *PTCH1*. This contrasts with 7 in 1199 healthy controls ($p = 0.0008$, odds ratio of 5.6 (95% Confidence interval 2.1–14.9)). The variants clustered at the 3′ end of the gene and have not been associated with Gorlin syndrome or other phenotypes.

Zebrafish embryo studies of a recurrent de novo BEEC associated variant c.4246T>C (p.Phe1416Leu) in *PTCH1* demonstrated that injection of mutant and wild type human transcripts resulted in a disrupted cloaca, whereas injection of wild type or mutant sequences alone resulted in no phenotype.

We present genetic and preliminary functional evidence that putative dominant negative variants in *PTCH1* result in BEEC in a subset of individuals. We predict that these variants result in disrupted hedgehog signalling, a process integral to urogenital and midline developmental processes.

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