Zebrafish *gon4la/b* mutants phenocopy the postnatal growth restriction and artery stenosis found respectively in *Gon4l* mutated cattle and *YY1AP1* mutated humans

斑馬魚 ***gon4la/b*** 的突變可以分別模擬牛上 ***Gon4l*** 突變造成的生長遲緩與人上 ***YY1AP1*** 突變造成的動脈狹窄

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YY1AP1 is derived from Gon4l segmental duplication. Its mutations are highly associated with an early onset disease, Grange syndrome. These patients with a bi-allele frame-shift mutation on *YY1AP1* were diagnosed with defects in their vasculatures, including artery stenosis, artery occlusion, chronic hypertension and stroke with *p21* overexpression. However, the mutation of Gon4l was reported to induce postnatal growth restriction in cattle.

Through bioinformatics analysis, we found that zebrafish *gon4la/b,* generated by the third whole genome duplication, are the homologs of human *Gon4l*/*YY1AP1*, where YY1AP1 is generated by random segmental duplication. *gon4la*$^{nn2121-/-}$ showed postnatal growth restriction with intestinal goblet cell reduction and perturbation in insulin-like growth factor. In contrast, the *gon4lb*$^{tu24-/-}$, an early stop *gon4lb* mutant, and *gon4lb*$^{nn2112-/-}$, a hypomorphic allele without PAH and SANT domains, showed artery stenosis/occlusion phenotype with *tp53* and *p21* overexpression. However, the circulation defect was not observed in the *gon4lb*$^{nn2122-/-}$, a *gon4lb* allele predicted to have no PAH and SANT domain, suggesting that *gon4lb* is the functional homolog of YY1AP1.

The expression of artery marker, *efnb2a*, and vein marker, *flt4*, was subsequently found to be compromised in the *gon4lb*$^{tu24-/-}$ with a reduction of *vegfc* expression, suggesting that the circulation defect in the *gon4lb* mutant could be a result of *vegfc* deficiency induced by the overexpression of *tp53*. Noticeably, an enrichment of Gon4lb on *tp53* promoter region and gene body was also found in a publicly available DamID-seq dataset, indicating that Gon4lb could modulate the expression of *vegfc* through its transcriptional regulatory role on *tp53*. To prove that, *tp53* was knocked down with *tp53* morpholino and the circulation defect was partially rescued and nearly fully rescued in *gon4lb*$^{tu24-/-}$ and *gon4lb*$^{nn2112-/-}$ mutants, respectively.

Even though the *gon4l* paralogs in zebrafish and mammals were produced by different mechanisms, the data shown above suggests that zebrafish *gon4la/b* is the functional homolog of mammalian *Gon4l*/*YY1AP1*, respectively. Gon4la may alter the growth phenotype through its function in hormone-secreting and/or digestive organs; while Gon4lb could modulate the development of vasculature through transcriptionally regulating the expression of *tp53*.