



## VGLL4, Far More than a Tumor Inhibitor

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### DESCRIPTION

The vestigial (*vg*) gene was first discovered in *Drosophila* and its homologues were subsequently identified in vertebrates and called Vestigial like member 14 (VGLL14) [1]. The VGLL proteins, act as transcription cofactor, interact with the transcription factor TEAD and MEF *via* a conserved TDU domain [2,3]. Among them, VGLL4 contains two TDU domains that can competitively bind TEAD with YAP, thereby inhibiting YAP downstream target genes and suppressing cell proliferation [3,4]. Therefore, VGLL4 is considered as a tumor suppressor and has been widely studied and reported [5,6].

To further explore the function of VGLL4, we constructed the first VGLL4 mutant mouse line and found that the VGLL4 total knockout mice died within 24 hours after birth [7]. Subsequently, tissue-specific knockout of VGLL4 was extensively investigated. We first found that specific knockout of VGLL4 in endothelial cells leads to excessive proliferation of interstitial cells after EMT transformation of heart valves in embryonic mice, resulting in valve thickening and ultimately abnormal cardiac function in adult mice [7]. Selective knockout of VGLL4 in muscle satellite cells significantly promotes their proliferation while inhibiting differentiation, leading to delayed muscle regeneration [8]. On the other hand, conditional knockout of VGLL4 in osteoblasts results in osteoporosis and a phenotype resembling craniofacial dysplasia due to osteoblast differentiation disorders [9]. Shortly after, another mutant mouse line exhibiting the same phenotype was reported, along with findings indicating that knockout of VGLL4 in mouse cardiomyocytes does not affect heart development [10]. However, the underlying cause of the postnatal lethality observed in VGLL4 knockout mice remains unclear.

In order to gain insights into gene function and the phenotype of gene mutations, it is often useful to investigate when and where a gene is expressed in the organism. One approach to determine the pattern and timing of gene expression is through the use of reporter genes which introduced upstream or downstream of the coding region of the gene, or through the

conditional CreER/loxP (DreER/rox) system, in which tamoxifen induced CreER fusion protein excision of the loxP-flanked STOP (loxP-STOP-loxP) cassette upstream enables downstream reporter expression driven by ubiquitous promoter [11,12]. These regulatory sequences control which cells express a gene and under what conditions, and can also be used to drive the expression of a reporter gene. Therefore, we generated the Vgl4-GFP and Vgl4-DreER mouse lines. In the Vgl4-GFP line, the expression of the VGLL4-GFP fusion protein is driven by the endogenous Vgl4 promoter. The level, timing, cell location and cell specificity of GFP protein reflect the action of the VGLL4 [7]. As for the Vgl4-DreER line, which utilizes the Dre/rox system, it not only can be combined with a routine rox-STOP-rox-reporter cassette to induce the expression of reporter genes after tamoxifen administration, labeling VGLL4 expressing cells *in vivo*, but is also useful for combining with the CreER/loxP system and upgrade into a dual-recombinase system (such as loxP-STOP-loxP-GFP-rox-STOP-rox-RFP and loxP-STOP-loxP-rox-STOP-rox-RFP cassette and so on) to trace a specific VGLL4 positive cell population after introduce another cell specific CreER line, during development and pathological conditions [13,14]. Additionally, it also can be combined with the loxP-STOP-loxP-rox-STOP-rox-DTR-RFP cassette to delete specific VGLL4 expressing cell populations *in vivo* after tamoxifen and DT treatment, or to conditionally delete genes flanked by rox sites.

Our further application of the Vgl4-DreER mouse line may focus on two aspects. One is labeling and tracing specific VGLL4 positive cell populations during development, especially in the perinatal to postnatal stage, consistent with the results of Vgl4-GFP line, to disclose the postnatal VGLL4 expression map in different organs and pave the way to investigate potential postnatal lethality clues. The other is to observe the expression profile of VGLL4 under pathological conditions and to manipulate VGLL4 expressing cell population *in vivo*, and explore its function in diseases beyond tumorigenesis. We believe that the new function of VGLL4 will be reported successively in the near future.

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