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GATA4 Novel Role in Dilated Cardiomyopathy: Is the Drastic Zinc Finger Mutation Hiding a Non-DNA Binding Role for Zinc Finger Transcription Factors?

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GATA4 is a transcription factor that belongs to the GATA family of zinc finger proteins, which are expressed in various organs during mammalian development including the hematopoietic system, the heart, the gonads, the lungs, and the kidneys [1]. All vertebrate GATA family members have two zinc finger domains. The C-terminal finger serves as a DNA-binding domain and an interface of interaction with other transcription factors such as NKX2.5 and TBX5. The N-terminal domain, which is thought to have been acquired by duplication of the C-terminal domain through evolution, helps in stabilizing the binding to the DNA, and so far has been implicated in the physical interaction with the Friend of GATA (FOG) zinc finger proteins [2-4].

The GATA4 claim to fame has been through its role in the heart. Indeed, over the past 20 years, it has been one of the most rigorously studied transcription factors involved in cardiac development. GATA4 precedes some of the earliest cardiac differentiation markers during embryogenesis. It then goes on to play a vital role in cardiogenesis, and maintains it's importance in the postnatal-heart period [1,5]. Some of the functions of GATA4 include mediating differentiation, survival, and/or proliferation of terminal cardiac cells. It is also involved in mediating NPPA and NPPB signaling, and playing an essential role in the regulation of quintessential cardiac genes like Troponin C and I, myosin light chain-3, slow myosin heavy chain 3, m2 muscarinic acetylcholine receptor, and much more. Even more impressive is the list of the GATA4 cofactor entourage; HAND2, MEF2C, NFATC4, NKX2.5, TBX5, p300, ZFPM1/2, to name a few [1,4,6].

It's not surprising at all then, that mutations in *GATA4* have been implicated in such a vast array of Congenital Heart Disease (CHD) conditions. In humans, *GATA4* has been directly linked to cases of ASD, VSD, ECD, PS, TOF, DORV, TA, CoA, TGA, AF [6-9]. These results were the fruit of studies done in various animal models, which not only accentuated the importance of GATA4 in heart development, but also unraveled a role for GATA4 in the heart's physiological response to stress.

In the late 90's, research using rat models to understand the effect of pressure overload on the heart identified GATA4 as an integral gene in the heart's physiological hypertrophic response [10,11]. Since then, many *in vivo* and *in vitro* studies in rats and mice have confirmed the role of GATA4 in cardiac hypertrophy [12]. Loss of function mutation in mice resulted in their inability to undergo physiological hypertrophy in response to pressure overload [13]. Gain of function on the other hand, resulted in hypertrophic cardiomyocytes *in vitro*, and *in-vivo*, it resulted in the up-regulation of hypertrophic pathways as well as an increase in the heart to body weight-ratio in animals not exposed to pressure overload [14].

Li et al. have recently reported a mutation in *GATA4* in a family with dilated cardiomyopathy. They report a c.812G>C autosomal dominant missense mutation that resulted in a p.C271S substitution in the amino acid sequence [8]. The mutation falls in the second zinc finger domain of the GATA4 protein. The authors showed that it segregated completely with the DCM phenotype and that it had 100% penetrance.

Functional studies carried out by the authors showed that this mutation decreased GATA4's ability to up regulate downstream target genes, in addition to decreasing GATA4's synergistic transactivational activity with NKX2.5.The same lab published a second article that identified another mutation in *GATA4's* second zinc finger domain [15]. This time, a p.V291L mutation segregated with the phenotype and had 100% penetrance in a family with DCM. Similarly, functional analyses showed that the mutation decreased GATA4 ability to activate downstream genes. However, no mention was made of this mutation inhibiting GATA4's synergistic transactivational activity with NKX2.5.

Were as all previous work has implicated GATA4 in cardiac hypertrophy, the authors of both papers provided evidence that GATA4 is also involved in maintaining structural integrity of the heart vis-a-vis dilated cardiomyopathy. Previous work had shown that loss-of-function in *GATA4* resulted in cardiomyocytes that failed to hypertrophy in response to pressure overload. Put simply, when GATA4 function decreases, so too does the hearts cells' ability to hypertrophy. Both these papers make the claim that loss of function mutations in GATA4 resulted in dilated cardiomyopathy. Though the two processes of hypertrophy and dilatation of the heart are not mutually exclusive, they are certainly distinct. And while it is clear in both papers that the mutation of *GATA4* segregated with the DCM phenotype, it is not quite clear how a loss of function mutation of GATA4 resulted in DCM.

In both papers, the authors seem to allude to the transcription factor partners of GATA4 to try to explain this phenomenon. Indeed, in Li et al.'s paper, the authors point out that "mutations in the transcriptionally cooperative partners of GATA4, including NKX2-2 and TBX20 have been associated with familial DCM". However, *Li et al.* provided no evidence that the reported GATA4 mutation affected either the GATA4/NKX2-2 or the GATA4/TBX20 interaction. Rather, the *Li et al.* paper showed that only the interaction of GATA4/NKX2.5 is affected by the reported mutation.

The documentation of the GATA4 mutation provided by both papers is persuasive.

The PCR shows a clean heterozygous mutation, and the genotype segregates completely with the DCM phenotype. Taken alone, it seems quite reasonable to implicate GATA4 in DCM. However, taken in the context of the documented functions of GATA4, such a conclusion might seem hurried, especially in the absence of functional studies that directly link GATA4 loss of function to DCM.

It is important to note that both novel mutations affect the C-terminal zinc finger domain, which is the major functional part of the protein. And, with these mutations causing a major loss of function in the GATA4 protein as reported in both papers, one would expect the observed DCM phenotype to be paralleled in *GATA4+/-* mouse models. However, *Gata4 +/-* mice only have septal defects, and they develop no additional phenotypes in adulthood.

And while there could be a link between GATA4 and DCM, both papers fall short of explaining it. It could indeed be the case that the loss-of-function mutation of GATA4 causes DCM either through affecting GATA4 interaction with one of its known cooperative partners, or, more distally, its downstream transcriptional targets. The known partners are not directly involved in DCM except for a new report showing that *NKX2.5* mutations are present in only one family with adult onset DCM [16]. Conversely, mutations in some of the target genes like *ANKRD1*, and *LRRC10* are found to be disease causing [17,18]. This path however entails that other targets regulated at the transcriptional level must also be equally affected, thus one would expect to have other congenital defects in patients with the reported mutations that cause DCM. And while ASD is present in both families, the fact that it affects only 3 of the described 7 members with DCM points to an additional or altogether different hypothesis. Such a hypothesis could entail the possibility that the mutant protein now has a higher affinity towards a yet unidentified partner that has a direct role in the onset of DCM. Such a protein could be nuclear or even cytoplasmic and this entails assessing the cellular localization of the mutated GATA4 proteins. Ultimately a two-hybrid yeast screening will be essential to identify such partners using both the wild type and the mutated protein as bait.

The amazing progress made in the last 20 years in the field of cardiac development and disease relied mostly on the study of transcription factors like GATA4. We believe that data from population genetics will re-orient our view of cardiac diseases in general towards a global approach that integrates genomics, proteomics, and metabolomics.

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