



## Comparative *In silico* Analysis of Hypertrophic Cardiomyopathy Heart in Human and Normal Chicken Heart

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**Abstract:** Hypertrophic Cardiomyopathy (HCM) is an incurable disease, which causes excessive thickening of the myocardium. HCM is caused by abnormalities in genes which code for the proteins responsible for contraction of the heart. The anatomical resemblances between the Chicken heart and HCM heart are thickening of the muscle of the left ventricle, localized ring- like thickening of muscle under the aortic valve, and poorly formed anterior ventricular groove, and left ventricle projecting beyond the right ventricle. The mutations for the genes are retrieved from the databases: Human Genome Mutation Database, Familial Hypertrophic Mutation Database and Cardiogenomics databases. Since the Beta-myosin Heavy Chain (MYH7) is more predominant in causing HCM, that gene alone is taken and compared with normal chicken heart *myh7* gene. The amino acids were aligned by CLUSTAL W and they were found to have sequence homology of 85%. The phylogenetic tree was constructed by using PHYLIP to study evolutionary linkage. According to the results, it can be presumed that the chicken normal gene, during the evolutionary process have undergone many modifications and evolved as a complicated and advanced human heart.

**Keywords:** Hypertrophic Cardiomyopathy; Beta-myosin Heavy Chain; CLUSTALW; Phylogenetic tree.

### 1. Introduction

Birth defects are defined as abnormalities of structure, function and metabolism of the body that are evolved at birth. These abnormalities lead to mental or physical disabilities or even fatal [1, 2]. In fact, according to the March of Dimes, about 60% of birth defects have unknown causes [3]. The known factors are caused by environment or genetic factors or a combination of the two. In particular, congenital heart defects are the most found birth defects generally [4]. There are different types of congenital heart malformations; one of the most common diseases is Hypertrophic Cardiomyopathy (HCM). The HCM heart is characterized as thickening of the left ventricle muscle, localized ring like thickening of muscle under the aortic valve poorly formed anterior ventricular Chicken heart. In HCM, the muscle thickening occurs

without an obvious cause. The thickened muscle usually contracts well and ejects most of the blood from the heart through the muscle in HCM is often stiff but relaxes poorly requiring higher pressures than normal inflow of blood to expand. The amount of blood which the heart can hold is therefore reduced and this, in turn, will limit the amount of blood which can be ejected with the next contraction [5, 6]. In addition, microdissection of the heart muscle with HCM shows that it has an abnormal arrangement of contractile filaments and the normal alignment of muscle cells is absent and this abnormality is called myocardial disarray. In the majority of cases, the condition is inherited [7-11]. It was found that totally 26 genes were involved in this disease. Myosin Heavy chain (MYH7) is the most predominant genes found mutated in the HCM patients [12].

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## 2. Materials and Methods

The nucleotides of complete coding sequences of the genes causing the HCM disease were obtained from the National Center for Biological Information (NCBI) and the amino acid sequences were obtained from the SwissProt protein database (<http://www.expasy.org/sprot/>). For structure analysis of *myh7* protein, structural sequences and their details were obtained from mod base databases. Since *myh7* has been more predominant in causing HCM, that gene alone has taken and analyzed for both chicken and human from the ENSEMBL Genome Browser. The chicken *myh7* gene ENSEMBL Accession no. is ENSGALG00000013781 and the human gene Accession no. is ENSG00000092054. The mutations for the gene *myh7* are retrieved from the Human Genome Mutation Database (HGMD), Familial Hypertrophic Cardiomyopathy Mutation Database (FHCMD) and Cardio genomics database. The normal

and the mutated amino acid sequences of human *myh7* and the normal *myh7* chicken gene were aligned using clustalW multiple sequence alignment tool. A phylogenetic tree is a specific type of cladogram where the branch lengths are proportional to the predicted or hypothetical evolutionary time between organisms or sequences [13]. These phylogenetic trees were constructed by using the software PHYLIP.

## 3. Results

### 3.1 Alignment results

The normal and the mutated amino acid sequence of the *myh7* in human and the normal sequence of the chicken were taken and aligned using ClustalW. The alignment results showed maximum conserved regions except for a few nucleotides which meant that the mutated gene of the Human is highly similar to the normal chicken gene *myh7* (Fig. 1).

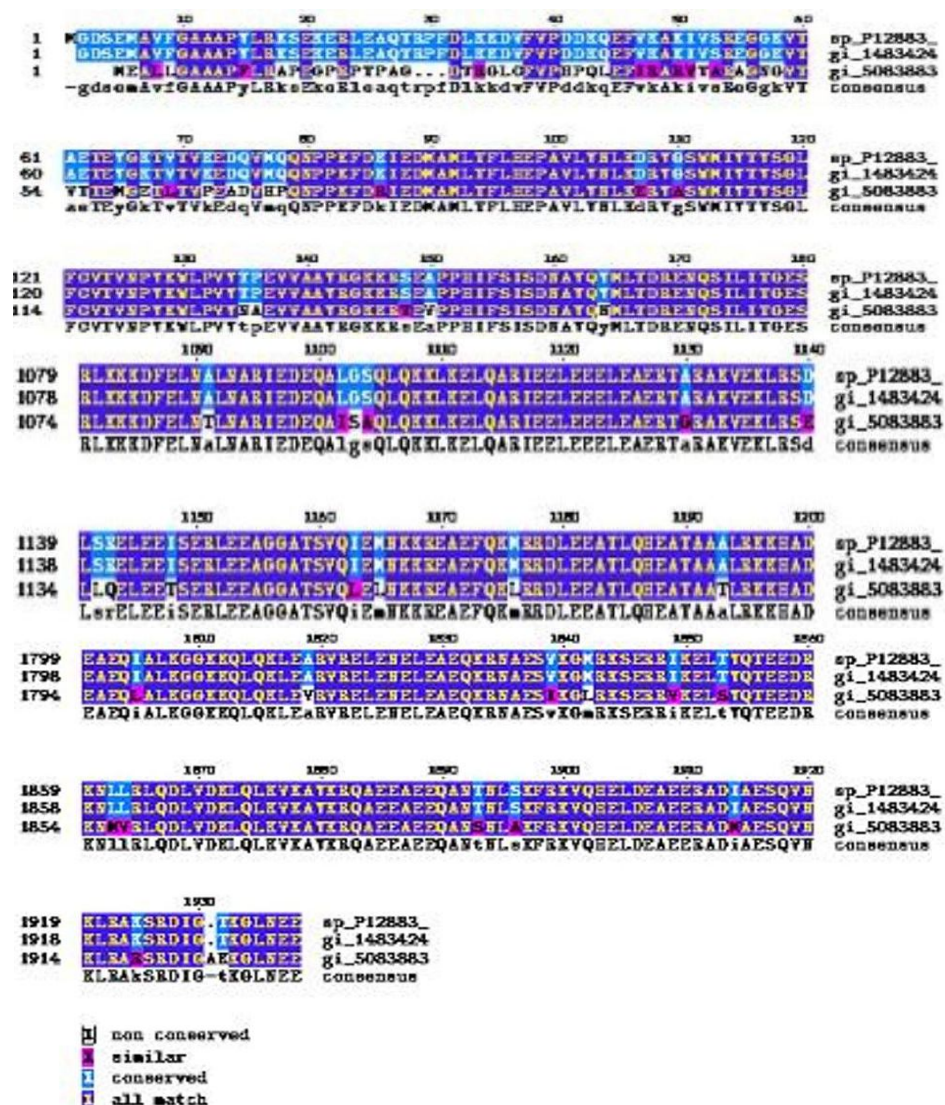


Fig. 1. Alignment results of normal *myh7* protein sequences of Human and chicken with mutated *myh7* Protein.

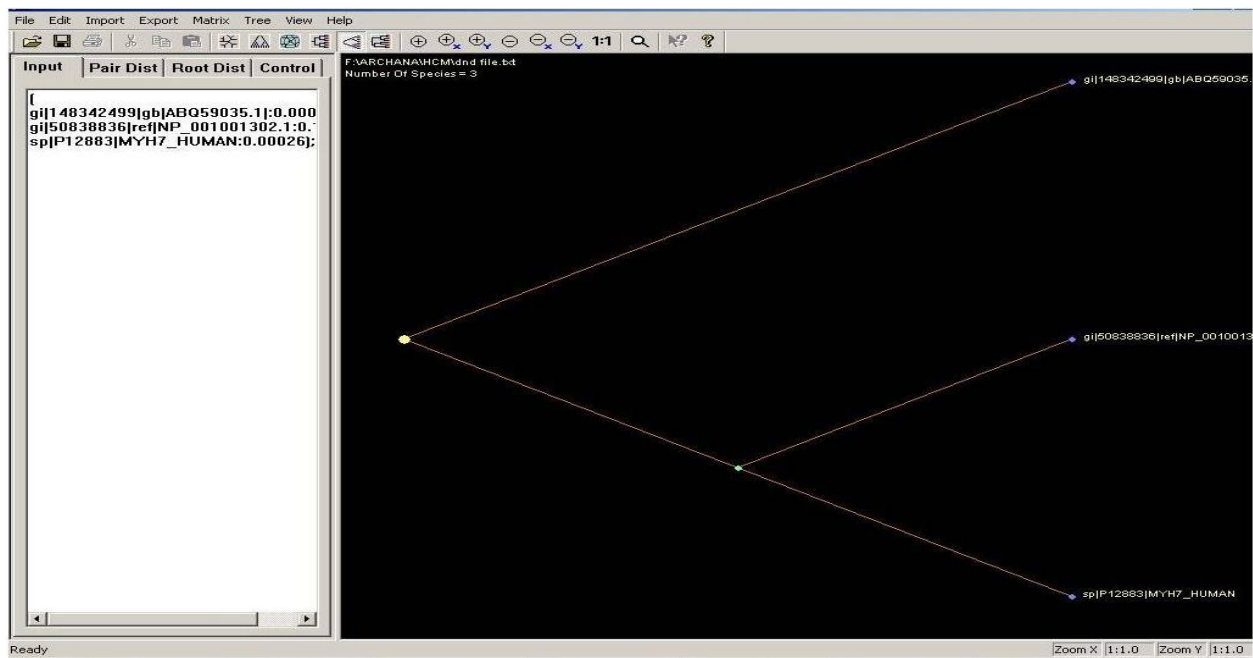


Fig. 2. Rooted phylogenetic tree.

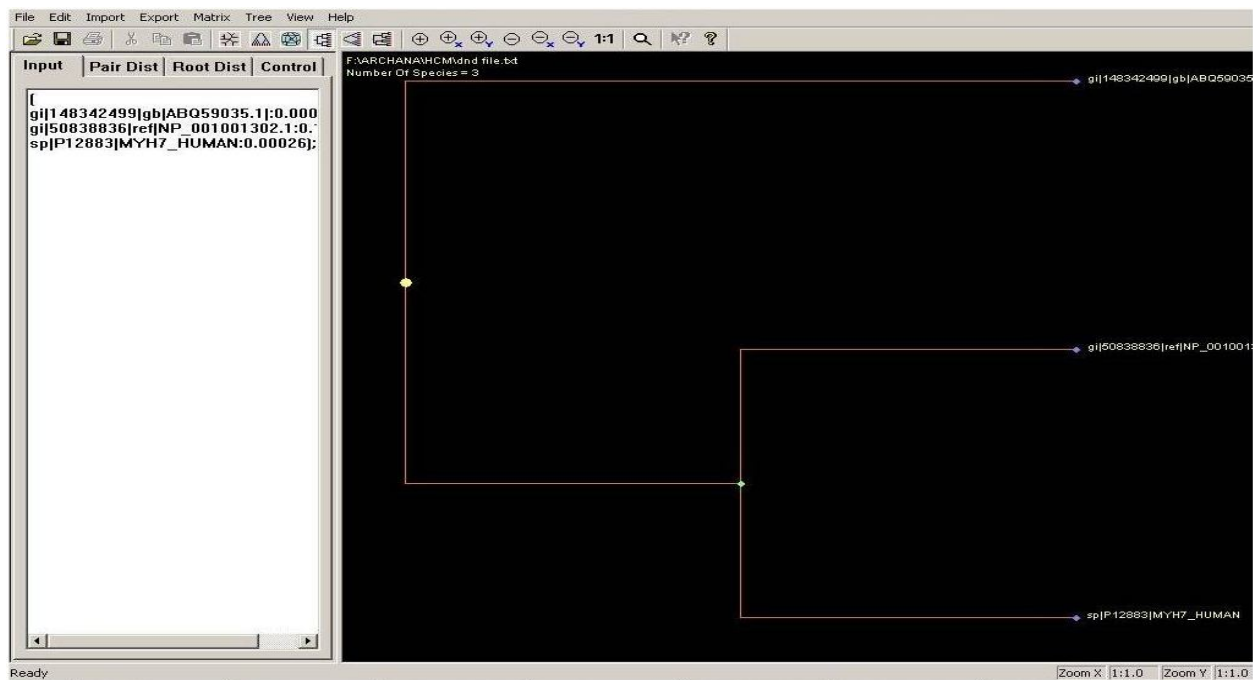


Fig. 3. Unrooted Phylogenetic tree.

### 3.2 Graphical Phylogenetic Tree

Phylogenetic trees were constructed using the Phylip online software package for both amino acid sequences of *myh7* protein of human and chicken. From the phylogenetic trees, it can be understood that the normal chicken *myh7* gene has sequence similarity and an evolutionary linkage with mutated Human *myh7* (Fig. 2 and Fig. 3).

### 4. Conclusion

According to the results, it can be inferred that normal chicken gene has undergone many modifications during evolution and evolved as a complicated and advanced human heart. Probably HCM-like condition might be an evolutionary defect, in cases like the *myh7* gene in some individuals has not completely evolved to support our body need and hence appear diseased. We have studied only a single gene,

the *myh7* but there are 25 genes more responsible for this HCM prevalence. Hence further study is needed to support the proposed theory. The important impact of this study is that the elaborate studies of evolutionary changes in the heart structure and function can give a solution for defining therapeutic drugs for this particular disease.

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### References

- [1]. Botto, L.D., Gnansia, E.R., Siffel, C., Harris, J., Borman, B. & Mastroiacovo, P. (2006). Fostering International Collaboration in Birth Defects Research and Prevention: A Perspective from the International Clearinghouse for Birth Defects Surveillance and Research. *Am. J. Public Health*, 96: 774 - 780.
- [2]. Wellesley, D., Boyd, P., Dolk, H. & Pattenden, S. (2005). An aetiological classification of birth defects for epidemiological research. *J. Med. Genet.* 42: 54 – 57.
- [3]. David, W.R. (2003). March of Dimes. *Arcadia Publishing*.
- [4]. Watkins, M.L., Edmonds, L., McClearn, A., Mullins, L., Mulinare, J. & Khoury, M. (2002). The surveillance of birth defects: the usefulness of the revised US standard birth certificate. *Am. J. Public Health*, 86(5): 731-734.
- [5]. Blaasaas, K.G., Tynes, T. & Lie, R.T. (2004). Risk of selected birth defects by maternal residence close to power lines during pregnancy. *Occup. Environ. Med.*, **61**: 174.
- [6]. Brent, R.L. (2004). Environmental Causes of Human Congenital Malformations: The Pediatrician's Role in Dealing with These Complex Clinical Problems Caused by a Multiplicity of Environmental and Genetic Factors. *Pediatrics*, 113: 957 - 968.
- [7]. Hagege, A.A. & Schwartz, K. (2003). Genetic basis and Geno-type Relationships in Familial Hypertrophic Cardiomyopathy. *Blackwell Futura Publications*.
- [8]. Ramirez, C.D. & Padron, R. (2004). Familial hypertrophic cardiomyopathy: genes, mutations and animal models. A review. *Invest Clin.*, 45(1): 69-99.
- [9]. Spirito, P. & Piccininno, M. (2003). Prevalence, prevention and treatment of Hypertrophic Cardiomyopathy, vol: 195, *Blackwell Futura Publications*.
- [10]. Mohiddin, S. & Fananapazir, L. (2001). Advances in understanding hypertrophic cardiomyopathy. *Hosp. Pract. (Minneap)*, 36(5):23-5, 29-30, 33-6.
- [11]. Cuda Fananapazir, G.L., Zhu, W.S., Sellers, J.R. & Epstein, N.D. (2003). Skeletal muscle expression and abnormal function of Beta-myosin in hypertrophic cardiomyopathy. *J. Clin. Invest.*, 91: 2861-2865.
- [12]. Van Driest, S.L., Ackerman, M.J., Ommen, S.R., Shakur, R., Will, M.L., Nishimura, R.A., Tajik, A.J. & Gersh, B.J. (2002). Prevalence and severity of “benign” mutations in the beta-myosin heavy chain, cardiac troponin T, and alpha-tropomyosin genes in Hypertrophic Cardiomyopathy. *Circulation*, 106(24):3085-90.
- [13]. Chen Yang and Sami Khuri (2003). PTC: An Interactive Tool for Phylogenetic Tree Construction, *Proceedings of the Computational Systems Bioinformatics (CSB'03)*.
- [14]. Venter, J.C., Adams, M.D., Myers, E.W., Li, P.W., Mural, R.J., Sutton, G.G., Smith, H.O., Yandell, M., Evans, C.A. & Holt, R.A. (2001). The sequence of the human genome. *Science*, 291:1304–1351.
- [15]. Check, E. (2002). Priorities for genome sequencing leave macaques out in the cold. *Nature*, 417: 473–474.
- [16]. Epstein, N.D., Cohn, G.M., Cyran, F. & Fananapazir, L. (2000). Differences in clinical expression of hypertrophic cardiomyopathy associated with two distinct mutations in the beta-myosin heavy chain gene. *Circulation*, 86(2):688-90.
- [17]. Rayment, I., Rypniewski, W.R., Schmidt-Base, R., Smith, R., Tomchick, D.R., Benning, M.M., Winkelmann, D.A., Wesenberg, G. & Holden, H.M. (1993). Three-dimensional structure of myosin subfragment-1: A molecular motor. *Science (Wash. D)*. 261: 50-5.
- [18]. Watkins, H., McKenna, W.J., Thierfelder, L., Suk, H.J., Anan, R., O'Donoghue, A., Spirito, P., Matsumori, A., Moravec, C.S., Seidman, J.G. & Seidman, C.E. (1995). Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. *N. Engl. J. Med.*, **332**: 1058-1064.
- [19]. Giribet, G. (2002). Current advances in the phylogenetic reconstruction of metazoan evolution. A new paradigm for the Cambrian explosion? *Mol. Phylogenet. Evol.*, **24**:345–357.
- [20]. Olson, M.V. (1999). When less is more: gene loss as an engine of evolutionary change. *Am. J. Hum. Genet.*, **64**: 18–23.