

# From modules to diseaseome: Human Wnt signaling pathway

Losiana Nayak and Rajat K. De

{losiana\_t, rajat }@isical.ac.in

Machine Intelligence Unit, Indian Statistical Institute, Kolkata-700108, India.

Keywords: Diseaseome, Modularization, Signal transduction

## Introduction

To understand mechanisms of various human diseases, a precise list of disease genes is not enough. A detailed map of cellular components, genes, transcription factors, RNAs, enzymes and metabolites, is much more helpful [1,2]. Diseases may not be independent of one another. More connected a disease is to other diseases, the higher is its prevalence and associated mortality rate [3]. A diseaseome wise study can help us to handle such situations. A diseaseome is the combined set of all known disorders or gene associations in a species. It is created by linking the complete set of genetic disorders with the complete list of disease genes [1].

Here we have tried to create such a disease map, from human Wnt signaling pathway. A module can be defined as a subset of a pathway that tends to be self-sufficient in function and tries to be minimally dependent on other modules of the pathway [4]. They can be created from a network, by graph partitioning and clustering techniques, but more preferably by modularization algorithm [4]. Members of Wnt signaling pathway have ubiquitous role in regulation of cell fate determination, growth, development, proliferation, migration, differentiation and apoptosis in various species. Abnormal functions of these members are responsible for a plethora of diseases like OPPG syndrome, Van-Buchem disease, skeletal malformation, autosomal dominant sclerosteosis and osteoporosis type I syndromes and cancers of various types (gastric, hepatic, skin, head and neck, lymph, blood, uterus, prostate etc.) among others [5,6].

As preventive research measure(s) to such diseases generally the effected genes are targeted, studied and researched. But the highlighting point is "if we target only gene A for disease B, and ignore the fact that gene A is part of a pathway/system that contains others genes (may be gene C to gene N), it will be playing with the single side of the coin. If the disease is a system level one, to crack the puzzle we need to study them from system level. For example in the above case, along with gene A, its neighbors and their behaviors in the system must be considered while searching for a cure to disease B and **what if these neighbors are again responsible for some other diseases? Are the diseases somehow related? Are they affecting each other's pathogenicity? Does one of them behave as a precursor to the other one(s)? Is there a single root to all of them?** These questions need to be answered when we go for a system level study and analysis. We need superior knowledge base(s) that can answer all these questions. Diseaseomes are such kind of knowledge bases.

## Method

Modularization is a process by which we can split a pathway into smaller sub-pathways that represent certain sub-function of the whole pathway. The human Wnt signaling pathway contains 60 members, linked among themselves by 70 relations, and gets modularized into 8 modules [Fig. 1] namely WNT16, (DVL1)1, AXIN1, CTNNB1, LEF1, (DVL1)2, PLCB1 and Tp53 [7]. Each module contained some members of the original pathway. An extensive literature mining of these members is done to get their associated diseases. To establish the human 'Wnt Signaling Pathway Diseaseome' [Fig. 2], we have denoted the links between a module and it's components with a straight line, and the links depicting the association between a component and its diseases are denoted with dotted lines.

## Results

- The human Wnt signaling pathway diseaseome is depicting the genes' and pathway behavior in disease(s) states [Fig. 2].
- Members of more than one module are linked, in that sense modules are not totally independent of each other (Ex: Module 3 and Module 5).
- A single disease may be associated with many members lying in the same module (Ex: Glioma in Module 1).
- A single disease may be associated with many members lying in different modules (Ex: Hepatocellular Carcinoma).

## Innovative aspects

- Pathway architecture studies help us to uncover potential knowledge about their overall function that contributes to cure human diseases.
- Disease maps are potential knowledge bases that throw light on multiple disease related complicacies.
- A disease network build from all the modules of the Wnt signaling pathway will throw light on its role in various diseases.

**Acknowledgement:** Losiana Nayak is grateful to Council of Scientific and Industrial Research, India, for providing her a Senior Research Fellowship.

## References

1. K. Goh et al. (2007) PNAS 104(21): 8685-90.
2. A. Barabasi (2007) N. Engl. J. Med., 357(4): 404-407.
3. D. -S. Lee et al. (2008) PNAS, 105(29): 9880-9885.
4. L. Nayak et al. (2007) J. Biomed. Inform., 40(6):726-749.
5. K. M. Cadigan et al. (2006) J. Cell Sci., 119(3):395-402.
6. D. Pinto et al. (2005) Biol. Cell; 97(3): 185-196.
7. R. K. De et al. (2008) in Proc. of HGM'08, Hyderabad, India (published as abstract).
8. V. Batagelj et al. url: <http://vlado.fmf.uni-lj.si/pub/networks/pajek/>.

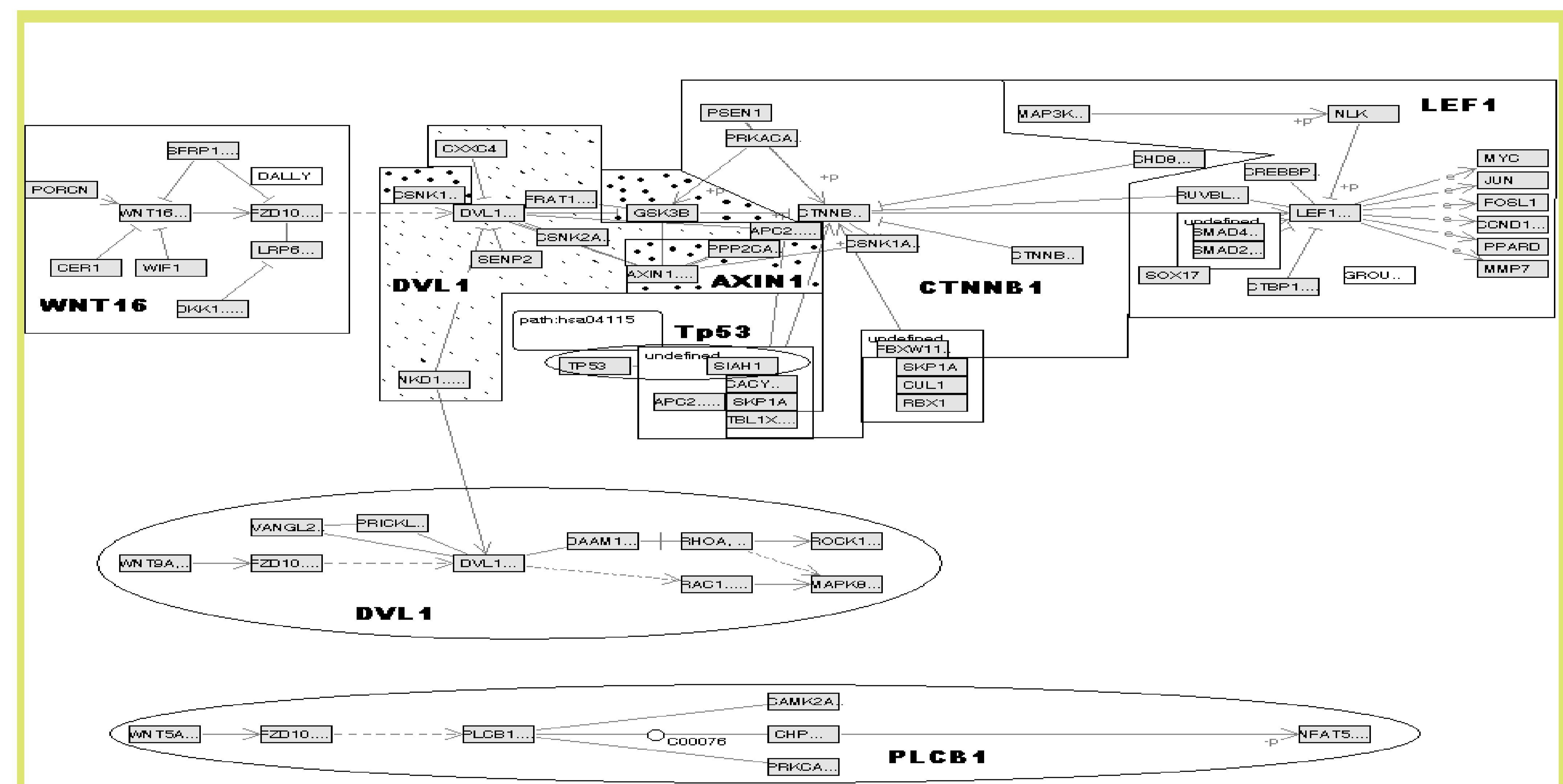


Figure 1: The modularized Wnt signaling pathway of *H. Sapiens* for  $c=3$

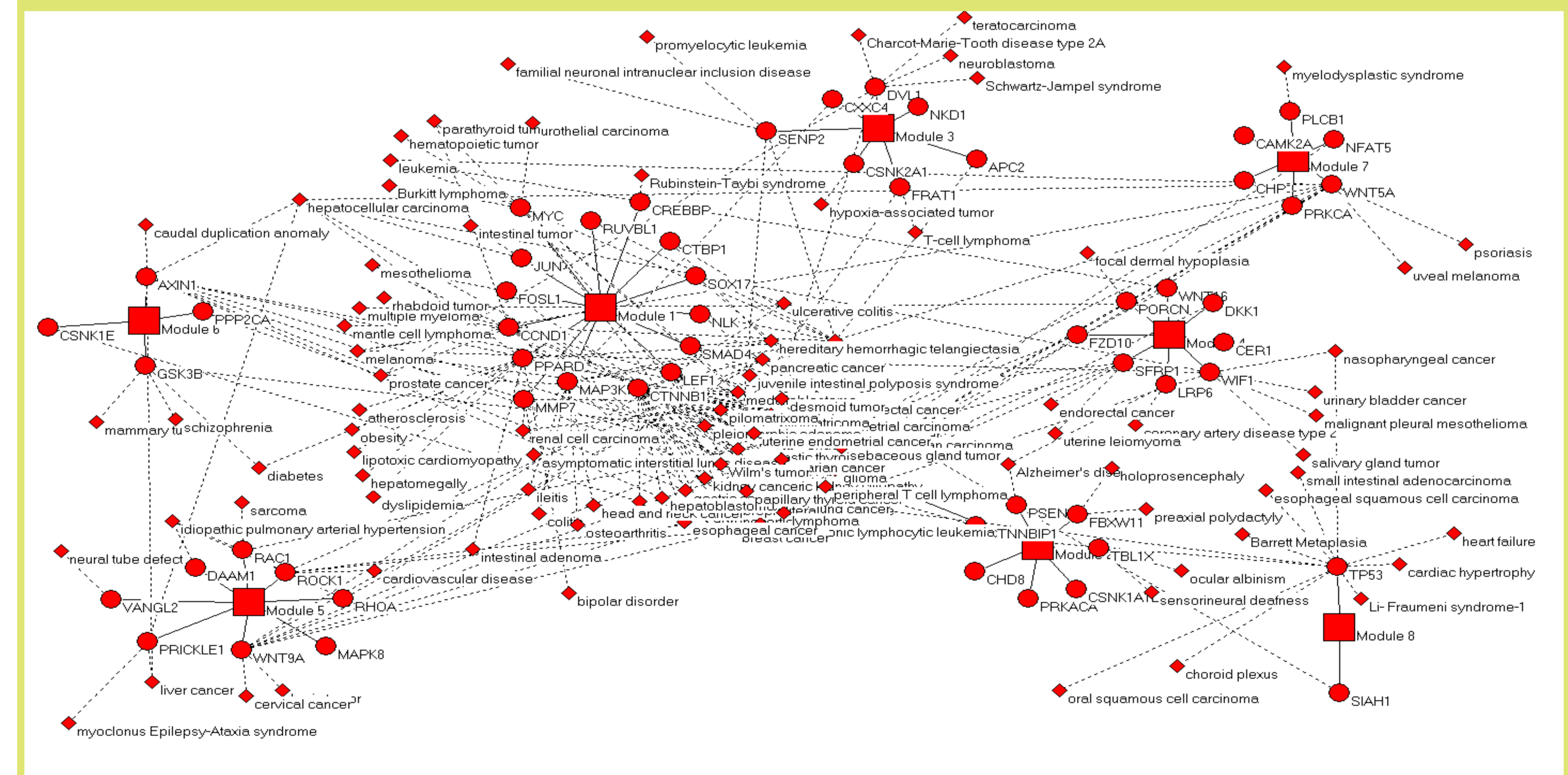


Figure 2: The Diseaseome of Human Wnt signaling pathway [Rectangles represent the modules obtained from human Wnt signaling pathway by Modularization algorithm, Circles represent the members of a module and diamonds represent the diseases associated with these members]