CHAPTER 2

7TM-CADHERINS:
Developmental Roles and Future Challenges

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Abstract: The 7TM-Cadherins, Celsr/Flamingo/Starry night, represent a unique subgroup of adhesion-GPCRs containing atypical cadherin repeats, capable of homophilic interaction, linked to the archetypal adhesion-GPCR seven-transmembrane domain. Studies in Drosophila provided a first glimpse of their functional properties, most notably in the regulation of planar cell polarity (PCP) and in the formation of neural systems. Details of the molecular and cellular functions of 7TM-Cadherins are slowly emerging but many questions remain unanswered. Here the developmental roles of 7TM-Cadherins are discussed and future challenges in understanding their molecular and cellular roles are explored.

THE 7TM-CADHERINS: A UNIQUE GROUP OF ADHESION-GPCRs

The 7TM-Cadherins are unique within the adhesion-GPCR family as their extracellular domains comprise a series of nine atypical cadherin repeats linked to a combination of EGF-like and Laminin G-like domains (Fig. 1). Cadherin repeats are repetitive subdomains which contain sequences involved in calcium binding and which are capable of homophilic interaction, for a review see reference 1. The cadherin superfamily consists of a number of subgroups which are of a classic and nonclassic type, for a review see reference 2. Classic cadherins interact with cytoplasmic catenins and are well-defined adhesion molecules whereas nonclassic cadherins, such as the protocadherins and 7TM cadherins, do not bind catenins and generally exhibit weak adhesive activities. The combination of EGF-like and Laminin G-like (LG) domains

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with cadherin repeats found within the extracellular domain of 7TM-Cadherins, is an ancient association and characterises many cadherin-containing proteins in invertebrates. Vertebrate classic cadherins, such as E-cadherin, have lost the EGF/LG region and, strikingly, differ from their invertebrate counterparts in both sub-cellular distribution and adhesive properties. The role of these domains in 7TM-Cadherins and other nonclassic vertebrate cadherins remains unclear.

**THE FAMILY TREE**

The 7TM-Cadherins are an evolutionary conserved gene family with homologues identified from ascidians through to mammals (Table 1). Initially identified in mouse and given the name *Celsr,* [C cadherin E EGF L laminin G-like S seven-pass R receptor],\(^{10}\) two groups then independently identified a gene in *Drosophila melanogaster* (*Drosophila*) which they named *flamingo*\(^{11}\) or *starry night.*\(^{12}\) Subsequently a family of 3 genes was identified in mammals; *Celsr1, Celsr2* and *Celsr3.*\(^{13-16}\) In avians only two homologues have been isolated; *c-flamingo1* (*c-fmi1*)\(^{17,18}\) and *c-flamingo3* (Formstone and Mason, unpublished) whereas in teleosts, a four-member gene family is known to exist including two *Celsr1* homologues.\(^{19,20}\)