### FICHE SUJET DE THESE

<table>
<thead>
<tr>
<th>Titre de la thèse :</th>
<th>Genetic bases of Sonic Hedgehog-deficient disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mots-clés :</td>
<td>Brain development, Shh, Rare disease</td>
</tr>
<tr>
<td>Directeur de thèse :</td>
<td>Valérie Dupé</td>
</tr>
<tr>
<td>N° de tél :</td>
<td>02 38 07</td>
</tr>
<tr>
<td>Mail :</td>
<td><a href="mailto:valerie.dupe@univ-rennes1.fr">valerie.dupe@univ-rennes1.fr</a></td>
</tr>
</tbody>
</table>

#### Contexte socioéconomique et scientifique (env. 10 lignes) :

Whole-Exome Sequencing (WES) is now used to identify disease-causing genes in the clinical laboratories. However, the relevance of WES in patient diagnosis for complex rare diseases is uncertain. This work is based on the experience we have gained on genetics of complex diseases, in which a variation in the same gene can lead to different phenotypes in the same family. The proposed research aims to explain incomplete penetrance and variable expressivity observed in these non-Mendelian rare diseases by characterising pathogenic combination of rare variants. Our group coordinates an international network of a brain development disease, which is caused by a dysfunction of the SHH signalling pathway (SHH-deficient disorder). SHH operates during early brain development where it induces appropriate dorso-ventral patterning of forebrain and eye-field. We, and others have identified 20 at-risk genes, which are all implicated in the regulation of SHH dosage during brain development. However, 70 % of SHH-deficient disorder cases still remain unsolved.

#### Hypothèses et questions posées (env. 8 lignes) :

The emergence of holoprosencephaly is related to the dysfunction of several signalling pathways involved in the formation of the forebrain. It means SHH, NODAL, FGF and NOTCH signalling pathways. Among them, SHH is a secreted molecule that plays a major role in holoprosencephaly. Our recent work using WES has shown that HPE patients present enrichment of rare variants in genes related to the SHH pathway. Our hypothesis is that Holoprosencephaly results of the addition of deregulations of several signals that lead to a failure of the SHH pathway to pattern ventral forebrain during early development.

#### Grandes étapes de la thèse (env. 12 lignes) :

- The list of causative variants and variant combinations will be enriched with Next Generation Sequencing-based analyses, which are routinely performed to investigate genetic basis of novel SHH-deficient disorder cases.
- The student will determine the molecular consequences of most relevant variants and their pathogenic combinations on SHH signalling pathway. For this, functional analysis of new candidate genes or variants will be performed in human cultured cells that are competent as well for production and excretion of SHH signal as for SHH-dependent cell signalling down to target gene expression.
- The student will take advantage of the ability of human somatic cells to reprogram into induced pluripotent stem (iPS) cells, which offers great opportunity to generate cerebral organoids. These organoids are able to recapitulate many aspects of brain embryonic development including those related to SHH-deficient disorders. It will be a powerful model to study pathophysiology of SHH-deficient disorders at molecular, cellular and developmental levels.
### Compétences scientifiques et techniques requises par le candidat (2 lignes):
The candidate must have a strong background in genetics and molecular biology. Interest in developmental biology and bioinformatics is an additional advantage.

### 3 publications de l’équipe d’accueil relatives au domaine (5 dernières années):

### Collaborations nationales et internationales:
- Filippo Santorelli, (IRCCS, Pisa, Italy). Our collaborator establishing Zebrafish models.
- Jurgen Knoblich (Veinna, Austria) who pioneered development of cerebral organoids.