# Formins in Human Monogenic Disease

Subjects: Genetics & Heredity

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Almost 25 years have passed since a mutation of a formin gene, DIAPH1, was identified as being responsible for a human inherited disorder: a form of sensorineural hearing loss. Since then, our knowledge of the links between formins and disease has deepened considerably. Mutations of DIAPH1 and six other formin genes (DAAM2, DIAPH2, DIAPH3, FMN2, INF2 and FHOD3) have been identified as the genetic cause of a variety of inherited human disorders, including intellectual disability, renal disease, peripheral neuropathy, thrombocytopenia, primary ovarian insufficiency, hearing loss and cardiomyopathy.

Keywords: formins ; genetic disease ; gene variants ; developmental defects ; actin

## 1. Introduction

The human formin family consists of fifteen members (**Figure 1**A), divided into seven subfamilies [1], many of which are co-expressed in many tissues. Formins are involved in the polymerization of monomeric actin into linear filaments [2][3]. All formins possess two characteristic domains: a formin homology (FH) 2 domain, which catalyzes actin polymerization, and an FH1 domain, which binds profilin to provide monomeric actin to the FH2 domain. The other regions and domains can differ between formin subfamilies and are involved in regulatory mechanisms or specific interactions with other proteins. In addition to regulating the actin cytoskeleton, formins bind to microtubules through the FH2 domain and regulate the acetylation and stability of microtubules, and their alignment with actin filaments [4][5].

Members of the human Diaphanous-related formin subfamily, which includes Diaphanous homolog (DIAPH) 1-3, are regulated through the interaction of the Diaphanous inhibitory domain (DID) at the N-terminal end and the Diaphanous autoregulatory domain (DAD) at the C-terminal region [1]. The transition between closed/inactive and open/active states is mediated by the interaction of the Rho-family GTPases with the DID, which releases its interaction with the DAD (**Figure 1**B). Other formins with similar regulation are Disheveled-associated activators of morphogenesis (DAAM) 1 and 2, formin-like (FMNL) 1-3, and FH1/FH2 domain-containing (FHOD) 1 and 3.

The mutation of some of the formin genes causes monogenic disorders, as is the case of *DIAPH1*, which was the first formin gene found to be linked to a human Mendelian disorder [6]. Alteration of seven formins genes (**Figure 2**) have been acknowledged to date by the Online Mendelian Inheritance in Man (OMIM®, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD, USA), https://omim.org; accessed on 20 September 2021) as meeting the criteria for consideration as a primary cause of human monogenic disorders [7][8]: *DIAPH1-3* [6][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36], *DAMM2* [37], *FORMIN2* [38][39][40][41][42] (*FMN2*) , *INVERTED FORMIN 2* (*INF2*) [43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][74][75][76][77][78][79][80][81][82][83][84][85][86][87][88][89][90][91][92][93][94] and FHOD3 [95][96][97][98][99][100] . The mutations or dysregulation of the other formins have not been demonstrated to be the primary cause of the phenotype, although they probably contribute to it [101][102]. Mutant formins can alter specific organs by affecting the functioning of specific types of cell (**Figure 3**A,B).

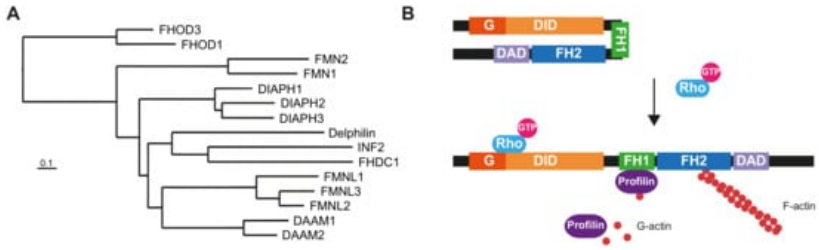


**Figure 1.** The human formin family. (**A**) Tree of human formins. The FH2 domain sequence of the formins was aligned with BLAST and the alignment was used to construct the tree [103]. The UniProt accession numbers of the corresponding

sequences were: DIAPH1 (O60610), DIAPH2 (O60879), DIAPH3 (Q9NSV4), DAAM1 (Q9Y4D1), DAAM2 (Q86T65), FMNL1 (O95466), FMNL2 (Q96PY5), FMNL3 (Q8IVF7), FHOD1 (Q9Y613), FHOD3 (Q2V2M9), FMN1 (Q68DA7), FMN2 (Q9NZ56), INF2 (Q27J81), FHDC1 (Q9C0D6) and Delphilin (A4D2P6). (**B**) Structure and regulation of Diaphanous-related formins. The interaction of the DID and the DAD maintains the formin in a closed, inactive conformation. The binding of a specific GTP-loaded Rho GTPase to the N-terminal region of the formin opens the molecule, rendering it in its active form. The FH1 domain recruits profilin, which feeds the FH2 domain with G-actin to form the actin filaments. The illustrated molecules are not drawn to scale.

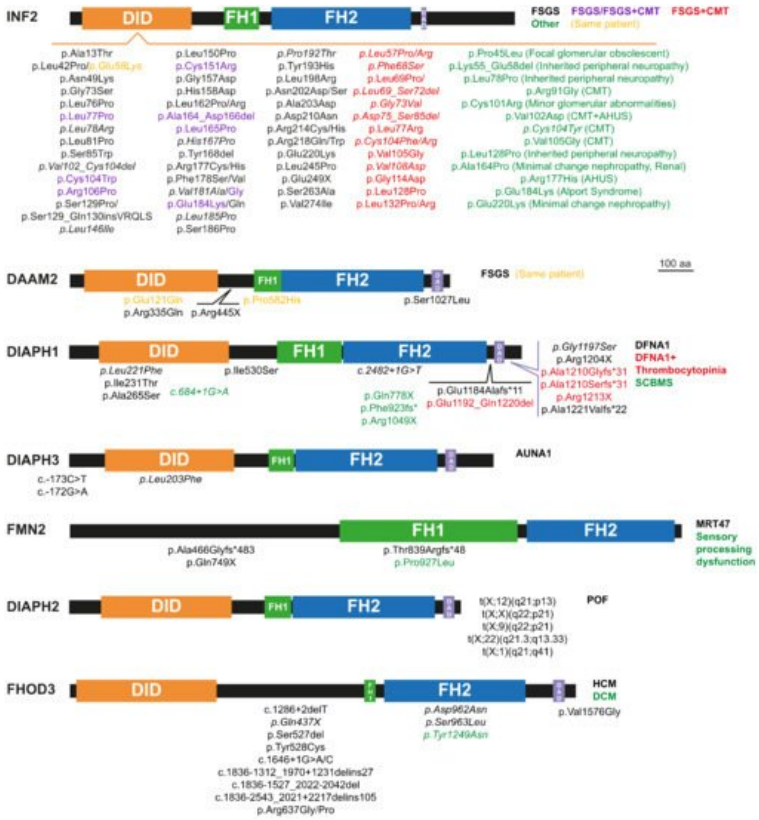


**Figure 2.** Pathogenic mutations of the formins causing monogenic disorders. Depending on the specific mutation, some formins produce different disorders. In these cases, we used the colors, as indicated, to refer to each of the diseases and the corresponding mutations. *, stop codon. The mutations without reported familial studies are indicated in italics.

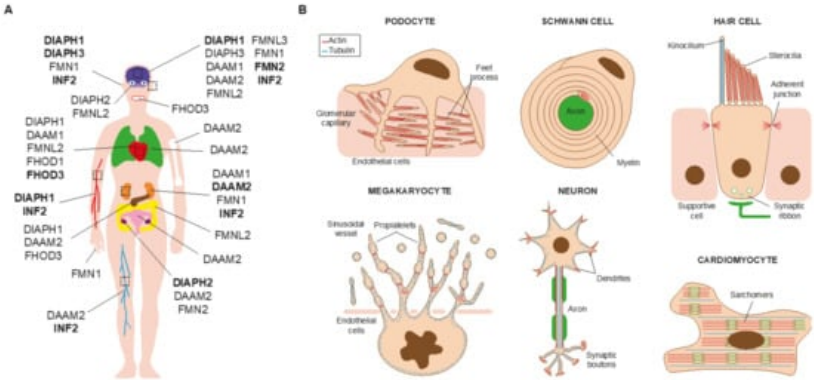


**Figure 3.** Some of the organs and cell types affected by formin alterations. (**A**) The formins involved in human disorders and the affected organs and systems are indicated in the schematic of the human body. Those causing monogenic disorders are highlighted in bold. (**B**) Some of the affected cell types. Their most characteristic structures are indicated.

## 2. Monogenic Disorders Caused by Formin Mutation

### 2.1. Nephrotic Syndrome and Charcot-Marie-Tooth Disease

Blood filtration and the concentration of metabolic waste into urine take place in the renal glomeruli. Podocytes are terminally differentiated cells that wrap around endothelial cells of glomerular capillaries by means of elaborate projections known as foot processes (**Figure 3**B). The contact between two of these processes forms a slit diaphragm, which is the structure responsible for blood filtration [104]. Deficient blood filtration causes nephrotic syndrome, which is characterized by proteinuria, hypoalbulinemia, hyperlipidemia, and edema, and can end in renal failure.

Focal segmental glomerulosclerosis (FSGS) refers to a histological lesion of scarred appearance present in localized regions of some, but not all, glomeruli [105]. The *INF2* gene is the formin for which the greatest number of pathogenic mutations has been described (**Figure 2** and Supplementary Table S8) [106]. *INF2* pathogenic mutations are autosomal dominant and produce FSGS (FSGS5, MIM: 613237) [43], which causes steroid-resistant nephrotic syndrome [107][108]. Depending on the specific mutation, FSGS co-occurs (or not) with Charcot–Marie–Tooth disease (CMTDIE, MIM: 614455) [48], which is a neuropathy affecting the functioning of the peripheral nerves that produces progressive distal muscle weakness [109]. All the INF2 disease-related mutations localize to the DID and the great majority are of the missense type. Genomic-wide screening (GWS) and whole-exome sequencing (WES) analyses in patients with renal disease identified a number of variants outside the INF2 DID [106] but, with the exception of a case of FSGS combined with CMT with a deletion in the DAD [94], it is not clear whether these variants are related to the pathogenic condition.

An in silico analysis of the effect of the pathogenic mutations indicates that they have a destabilizing structural effect in the DID [106]. This destabilization might affect the interaction of the DID with the DAD or with regulatory proteins [110][111], and results in gain-of-function of the actin polymerization activity of INF2. The case of a patient with combined FSGS and CMT has been described, in which a complete duplication of the *INF2* gene occurred, which represents further evidence of a gain-of-function phenotype in INF2-linked disease [93]. It is of note that the mutations causing combined FSGS and CMT are generally more destabilizing than those producing only FSGS, and that these two types of mutation distribute in the DID in a different manner, with the former being concentrated in the N-terminal half of the DID, whereas those causing only FSGS are distributed throughout the DID [106].

FSGS patients suffer a progressive loss of podocytes, which decreases the filtration capacity of the kidney. INF2-linked FSGS starts to become clinically relevant in adolescence or adulthood, causing glomerular dysfunction [107][108]. It is still not clear how INF2 mutations affect podocytes but, consistent with the enhanced actin polymerization activity of the pathogenic INF2 mutants [110], aberrant actin bundles have been observed in a renal biopsy of an affected patient [43]. Knock-in mice expressing the most common mutation, p.Arg218Gln, exhibit no apparent alteration in podocyte structure unless they are exposed to acute kidney injury [112]. This finding is consistent with the degenerative nature of INF2-related disease and suggests that FSGS might be the result of repeated kidney insults in individuals in which INF2 mutation makes them more prone to developing the disease. In addition to FSGS, *INF2* mutations have been found to contribute to, or be responsible for, other kidney conditions (**Figure 2** and Supplementary Table S8). In patients with combined FSGS and CMT, CMT symptoms appear in childhood, and renal damage appears earlier in life than in patients with only FSGS. In the cases with CMT, pathogenic INF2 affects Schwann cell polarization (**Figure 3**B), leading to abnormal myelin formation and/or maintenance [113][114]. The manifestation of FSGS alone is common in individuals with pathogenic INF2, but only one case of CMT has been described to date that makes the absence of accompanying renal disease explicit [59].

Recessive mutations of *DAAM2* (**Figure 2** and Supplementary Table S6), have recently been involved in nephrotic syndrome, type 24 (NPHS24, MIM: 606627) [37]. All the affected individuals presented FSGS with no extra-renal manifestations. The mutations were found in homozygosity in three individuals from consanguineous families, and in one individual with two different missense mutations from an outbred family. The missense mutations map to the region encoding the DID, the FH1 or the DAD, whereas the nonsense mutation maps immediately downstream of the DID and generates a truncated DAAM2 protein. The mutations at the DID and DAD appear to cause increased autoinhibition and, consequently, loss-of-function of actin polymerization activity. DAAM2, which is expressed by podocytes, colocalizes and associates with INF2 [37], suggesting the existence of crosstalk between the two formins that, given the link between INF2 and renal disease, may explain the renal damage caused by pathogenic DAAM2. Other formins might be involved in other kidney disorders. For instance, Fmn1 has recently been identified as a candidate modifier gene in X-linked Alport syndrome in mice, which is a genetic disease characterized by hearing loss, hematuria and, eventually, renal failure [115].

### 2.2. Hearing Loss

Hearing depends on the correct mechanostransduction of sound vibrations into electrical signals. This takes place in the organ of Corti, which is located in the cochlea in the inner ear. The cells responsible for this process are sensory epithelial cells, known as hair cells (**Figure 3**B), which possess dozens of stereocilia on their apical surface, formed of bundles of actin filaments [116]. Outer hair cells amplify the signal, and the perturbation activates the opening of ion channels at the stereocilia tips of inner hair cells, depolarizing the plasma membrane. This perturbation is subsequently transmitted by neurotransmitters released at the synaptic ribbon between the basolateral surface of hair cells and the auditory nerve. This generates electrical impulses in the latter that are transmitted to the brain, where they are decoded and analyzed in the auditory cortex. Given the importance of actin in the architecture of stereocilia, mutations in actin, actin-binding proteins, and the machinery involved in actin filament formation and function, including formins, can all cause hearing loss [117].

Sensorineural hearing loss is caused by dysfunction of the inner ear or the auditory nerve. Mutations in *DIAPH1* produce deafness, autosomal dominant 1 (DFNA1, MIM: 124900). In this disorder, auditory loss generally starts during the first decade of life, although there are cases with intrafamilial variability. Since the identification of a mutation in *DIAPH1* as the cause of sensorineural hearing loss in a large Costa Rican family [6], more families with a dominant pedigree caused by *DIAPH1* mutation have been described elsewhere in the world [11][12][13][18][19][21][22][23][24][25][26][27]. Affected individuals present frameshift or nonsense mutations or deletions near the DAD. These types of mutation create truncated forms of DIAPH1 that lack different segments of the carboxyl-terminal region of the molecule. In addition, more recently, missense mutations have been described at the DID and the coiled-coil downstream region and FH2 domain (**Figure 2** and Supplementary Table S3). The pathogenic p.Arg1204X mutation [21] results in early termination immediately before a basic amino acid motif ($RRKR^{1204–1207}$) present at the DAD C-terminus, which is important for the interaction with the DID [118]. This mutation partially relieves the autoinhibitory DID-DAD interaction, resulting in a mildly constitutive active molecule [21]. It is likely that this also occurs with other truncation mutations mapping around this site and with the missense mutations in the DID [119][120]. The *DIAPH1* gene mouse homolog, *mDia1*, is expressed in the organ of Corti during and after cochlear maturation, and localizes at the apical junctional complexes between the supporting cells and the hair cells [121]. As further evidence that hearing loss caused by *DIAPH1* mutations is due to gain- and not to loss-of-function, hearing progressively deteriorates in transgenic mice overexpressing wild-type mDia1 [121], whereas the hearing function of the *mDia*1 knock-out (KO) mice is not different from that of control mice [21]. The hearing defect in mice overexpressing mDia1 is associated with gradual loss of hair cells and the appearance of sparse and short or fused stereocilia cells [121]. A similar phenotype was observed in transgenic mice expressing the human Arg1204X mutant [21]. Increased gene dosage of *DIAPH1* has been documented in several cases of sporadic sensorineural hearing loss in humans [28]. These findings are further evidence that deafness-associated mutations of DIAPH1 cause disease by increasing actin polymerization activity, which causes the disorganization and dysfunction of stereocilia.

Auditory neuropathy, autosomal dominant, 1 (AUNA1, MIM: 609129) is characterized by abnormal or absent auditory brainstem responses but preserved cochlear outer hair cell function. A mutation (c.-172G > A) in a highly conserved GC element at the exon encoding the 5′ untranslated region of *DIAPH3*, was the first to be described as being involved in AUNA1. This mutation, which is probably of the gain-of-function type, results in 2- to 3-fold overexpression of *DIAPH3* mRNA and 1.5-fold overexpression of DIAPH3 protein levels. Consistent with increased levels of DIAPH3 as the cause of the auditory alterations, flies expressing a constitutively active form of Diaphanous, which encodes the sole Diaphanous-related formin in *Drosophila,* show an impaired response to sound [36]. Two reports found that mice overexpressing mouse mDia2, the murine homolog of human DIAPH3, present progressive impairment of inner hair cell stereocilia, whereas outer hair cells stereocilia and function were not generally affected in the specific mouse lines studied [122][123]. A reduction in the number of ribbon synapses was observed in one study [122], but not in the other [123]. Consistent with the role of formins in regulating microtubule dynamics, the microtubule meshwork undergoes aberrant targeting to the apical aspect of inner hair cells in transgenic mDia2 mice [123], probably contributing to stereocilia collapse. These mice also present early mortality due to cardiac defects, but no similar effect has yet been found in humans. In addition to the c.-172G > A mutation, other mutations causing AUNA1 have been described at the 5′ untranslated region of *DIAPH3* mRNA [35] and the DID of DIAPH3 [15] (**Figure 2**, Supplementary Table S5). Missense variants mapping to the DIAPH3 FH2 domain have also been found in patients with auditory neuropathy spectrum disorders [15][124], but it is not clear whether there they are pathogenic or simply rare variants.

In the case of *INF2* mutations associated with combined CMT plus FSGS, but not with FSGS alone, some of the patients also experience hearing loss [48][49][51][57]. Since INF2 mutations causing CMT affect peripheral nerve myelinization [113], auditory nerve damage is probably the cause of the hearing impairment, although hair cell stereocilia may also be affected, as in cases of *DIAPH1* and *DIAPH3* mutations.

### 2.3. Thrombocytopenia

The cell precursors of platelets, megakaryocytes, form extensions known as proplatelets, from which platelets are released into the circulatory system [125]. Macrothrombocytopenia is characterized by enlarged and reduced numbers of circulating platelets that can lead to inadequate clot formation and an increased risk of bleeding [125]. Platelet production begins with the extension of long membrane protrusions that are elongated by microtubule bundles to form proplatelet processes (**Figure 3**B). Amplification of the number of processes, which occurs by repeated bending and bifurcation, depends on actin filament formation [126][127][128]. It is controversial whether actin/microtubule crosstalk-induced proplatelet formation [126] or membrane budding without requiring proplatelet formation is the main mechanism of platelet formation in vivo [129].

Long after the discovery of the *DIAPH1* mutation as the cause of DFNA1, affected individuals were found to present asymptomatic thrombocytopenia and, sometimes, asymptomatic mild neutropenia (**Figure 2**, Supplementary Table S3),

which consists of abnormally low levels of neutrophils in the blood. The reduced platelet levels in these patients, the high content of polymerized actin, and the altered microtubule organization and stability observed in the platelets [27] are consistent with the requirement of DIAPH1 for proper proplatelet formation [130][131], and with previous works showing that DIAPH1 coordinates microtubules and the actin cytoskeleton [132][133]. It is of note that a moderate increase in the expression of DIAPH1 could be responsible for the thrombocytopenia associated with diseases caused by mutation in other genes, as may be the case for Roifman syndrome [134]. This is a rare, inherited disease (MIM: 616651) characterized by growth retardation, cognitive delays, skeletal malformations and immunodeficiency, and caused by mutation of the small non-coding RNA gene *RNU4TAC* [135].

Atypical hemolytic uremic syndrome (AHUS) is characterized by acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia (loss of blood cells through destruction). Two mutations in the DID of INF2 cause thrombocytopenia in the context of familial AHUS with (p.Val102Asp) or without (p.Arg177His) associated CMT [60]. In AHUS, the thrombocytopenia is due to platelet activation and consumption associated with blood cell destruction, rather than to an alteration in platelet production.

### 2.4. Microcephaly and Intellectual Disability

According to the Human Protein Atlas (http://www.proteinatlas.org; accessed on 30 August 2021), and consistent with the analyses of mouse brain [136], all the formins are expressed throughout the brain, generally with low regional specificity (Supplementary Table S2). Mutations of *DIAPH1*, *FMN2,* and *INF2* are associated, to varying degrees, with intellectual disability and neurodevelopmental disorders [137].

*DIAPH1* is expressed in neuronal progenitors during brain development [14]. Specific mutations of *DIAPH1* cause seizures, cortical blindness (vision loss due to a damage or malfunction in the part of the brain cortex responsible for processing visual information), and microcephaly syndrome (SCBMS, MIM: 616632) (**Figure 2**, Supplementary Table S3). In contrast to DFNA1-related mutations, SCBMS-associated *DIAPH1* mutations are generally of the nonsense type that affects the FH2 domain, are found in homozygosity, and are inherited with an autosomal recessive pattern, suggesting that they produce loss-of-function of DIAPH1 activity [10][14][16][17]. *mDia1* KO mice are not microcephalic but, instead, some mice present unilateral dilatation of the ventricles, indicating that the effect of these mutations is species-specific [14]. Unlike *mDia1* KO mice, *mDia2* KO mice present microcephaly and also hydrocephalus (accumulation of cerebrospinal fluid within the brain) [138]. This phenotype seems to be due to incorrect spindle assembly checkpoint regulation in cortical progenitor cells, causing massive loss of cortical progenitor cells, with the subsequent depletion of neurons [138]. *mDia1* and *mDia3* double-KO mice present hydrocephalus, but not microcephaly, due to the formation of a periventricular dysplastic (abnormal) mass during brain development [139]. The alteration of the actin cytoskeleton affecting the adherens junctions and progenitors' polarity seems to be the cause of the ectopic proliferation of neural stem cells in the double-KO mice. In addition to the characteristic SCBMS symptoms, some patients present pathologies related to immunodeficiency, such as recurrent infections, especially respiratory, bronchiectasis (enlargement of parts of the airways of the lung) and lymphoma [10][14][16]. Given that (i) *mDia1* KO mice show defects in T cell migration and activation [140][141], (ii) *DIAPH1* mutations are associated with mitochondrial dysfunction [10], and (iii) fibroblasts and some lymphocytes from SCBMS patients present mitochondrial alterations [10], it has been proposed that these additional symptoms are due to a defect in the mechanism of T cell activation [10].

A few cases of intellectual disability denominated mental retardation, autosomal recessive 47 (MRT47, MIM: 616193), are produced by mutations of *FMN2* [38][39][41][42] (**Figure 2**, Supplementary Table S7). The genomic alterations consist of homozygous frameshift and nonsense mutations that are always found in consanguineous families, and large de novo heterozygous deletions. One case with sensory processing dysfunction was also associated with a de novo missense mutation [40]. This phenotype is consistent with the role of FMN2 in stabilizing filopodia tip adhesions and regulating the chemotaxis of neuronal grown cones [142][143]. Unlike the effect of *FMN2* mutations in humans, *Fmn2* KO mice do not present any alteration in the brain [144]. However, double-KO mice of *FMN2* and *filamin A* show greater microcephaly severity and less neural progenitor proliferation compared with the phenotype of single *filamin A* KO mice. It has been suggested that this additive effect is a consequence of FMN2 and filamin A both forming part of the machinery of the endocytic route of the canonical Wnt pathway that regulates neural progenitor proliferation [145].

Mutations of other formin genes in addition to *DIAPH1* and *FMN2* have been associated with intellectual disability. In the case of *INF2*, some patients with FSGS and associated CMT, probably with severe mutations or an unfavorable genetic background, present intellectual disability and central nervous system anomalies [48][49][51]. An almost complete deletion of the *FMNL2* gene has been associated with a case of mental retardation [146]. However, since the patient also presented haploinsufficiency in *NR4A2*, a gene involved in the cerebral dopaminergic system, it is difficult to ascertain whether the disorder is caused by one or both mutations.

### 2.5. Primary Ovarian Insufficiency

*DIAPH2* has been implicated in premature ovarian failure (POF2A, MIM: 300511), also known as primary ovarian insufficiency, which manifests as premature menopause [29][30][31][32][33][34]. The patients generally present translocations of the X chromosome region that includes *DIAPH2* (**Figure 2**, Supplementary Table S4). This gene might be involved in the development of gonads since it is expressed in the ovaries and testes of mouse embryos [29], and, indeed, some of the patients present ovarian dysgenesis (abnormal development) [33][34]. Underlining the importance of DIAPH2, *Drosophila* with mutations in *Diaphanous* are sterile due to cytokinesis failure that affects spermatogenesis in males and follicle cell division in females [147].

Consistent with the possibility that formin genes other than *DIAPH2* are related to POF, *FMN2* has been associated with POF and infertility in mice and in human patients [148][149]. Female *Fmn2* KO mice exhibit defects in spindle positioning during meiosis I [144], which explains their low fertility. It has been proposed that upregulated levels of FMNL2 in humans also have a role in female infertility and gynecological health since they promote adenomyosis, which is characterized by the ectopic growth of the endometrium in the uterine walls, which are formed by the myometrium [150].

### 2.6. Cardiomyopathy

Thirteen out of the fifteen formins are expressed during postnatal development of the heart in mice within a specific timeframe that suggests a role for each formin in this process [151]. *FHOD3,* which is mainly expressed in the heart and regulates actin assembly in cardiomyocytes [152] (**Figure 3**B), has been linked to cardiac pathologies [153]. *FHOD3* mutations have been associated with hypertrophic (CMH28, MIM: 619402) [95][96][97][98][99][100] and dilated cardiomyopathies [154] (**Figure 2**, Supplementary Table S9), which are conditions in which the walls of the heart becomes thicker and stiff, and where the heart is enlarged, respectively. As a consequence of these alterations, blood is pumped less effectively. Two intronic variants of *FHOD3* have also been related to hypertrophic cardiomyopathy development [155] and a conservative substitution (p.Val1151Ile) with a reduced risk of dilated cardiomyopathy [156]. *Fhod3* KO mice present embryonic lethality due to defects in cardiogenesis and in neural tube closure [157], whereas conditional KO mice show that the FHOD3 protein is needed not only for prenatal and postnatal heart development, but also for its maintenance, since adult mice present cardiomegaly and mild impairment of cardiac function [158]. Transgenic mice expressing FHOD3 defective in actin binding have a similar phenotype to that of dilated cardiomyopathy patients [157]. It is likely that the specific domain affected by the mutation, as well as the individual genetic background, could determine the appearance of one or other pathology, although both appear to be inherited in an autosomal-dominant manner. Angiotensin II is an important factor causing blood pressure overload-induced cardiac hypertrophy [159]. In cultured rat cardiomyocytes, angiotensin II signaling regulates FHOD3 activation through phosphorylation of its C-terminal region by ROCK kinase, raising the possibility that pathogenic FHOD3 causes heart hypertrophy by this mechanism [160].

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