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Review

Inositol 1,4,5-Trisphosphate Receptors in Human Disease: A Comprehensive Update

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Abstract: Inositol 1,4,5-trisphosphate receptors (ITPRs) are intracellular calcium release channels located on the endoplasmic reticulum of virtually every cell. Herein, we are reporting an updated systematic summary of the current knowledge on the functional role of ITPRs in human disorders. Specifically, we are describing the involvement of its loss-of-function and gain-of-function mutations in the pathogenesis of neurological, immunological, cardiovascular, and neoplastic human disease. Recent results from genome-wide association studies are also discussed.

Keywords: Alzheimer; ataxia; autoimmune disease; cancer; cardiovascular disease; diabetes; GWAS; IP3 Receptors; ITPRs; mutations

1. Introduction

Since their discovery in the 1970s, several studies have provided substantial evidence that inositol 1,4,5-trisphosphate receptors (ITPRs) play a pleiotropic role in the regulation of cellular functions. Indeed, their ability to regulate calcium handling poses ITPRs at the heart of molecular networks underlying cellular homeostasis: From proliferation, apoptosis, and differentiation to metabolism and neurotransmission.

ITPR was identified for the first time as a large membrane protein called P400 [1,2] that was able to regulate intracellular calcium spikes [1–3]. After protein purification and cDNA isolation, it became clear that P400 was a channel releasing calcium from the endoplasmic reticulum (ER) [4–6]. Later, ITPR was shown to be a rather peculiar channel, as two-second messengers are needed for its activation: IP3 and calcium [7–12].

Three isoforms of ITPR have been identified (ITPR13) in mammals, which, albeit produced by different genes, show 70% of homology in the primary protein sequence [13]. The similarity in amino acid sequence also reflects the resemblance in protein conformation and spatial organization. All three isoforms consist of five domains: Suppressor domain (SD), IP3 binding core domain (IBC), regulatory domain, transmembrane domain (TD), and C-terminus domain (CTD) [14–17]. These domains are organized in a complex tetrameric "mushroom-like" structure (Figure 1), with the stalk inserted in the ER membrane and the cap exposed to the cytosol [18]. The stalk is mainly

represented by the transmembrane TM domain, with its six-helices forming the ion-conducting pore [16]. All the other domains are in the "cap", exposed to the cytosol. This organization makes the IBC domain available to IP3 binding, and the regulatory domain to the many interactions and post-transcriptional modifications that regulate the receptor activity, including phosphorylation and oxidation [16].

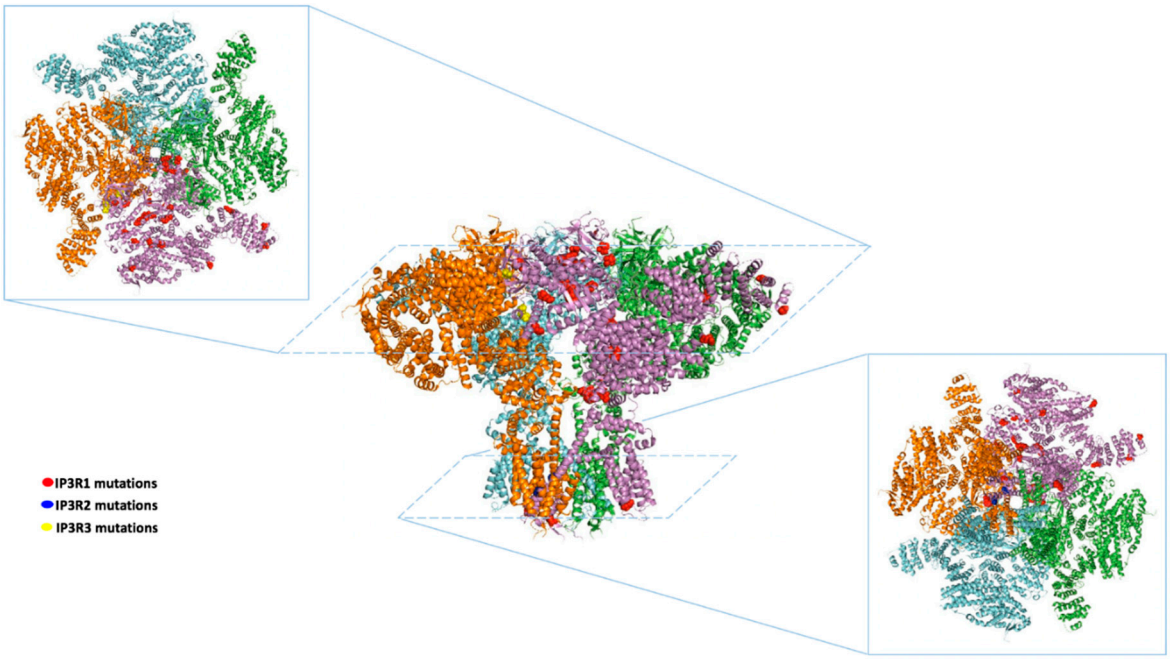

Figure 1. Representative structure of inositol 1,4,5-trisphosphate receptors (ITPRs) (1-3) showing disease-related mutations. In the middle, representative "mushroom-like structure" of ITPRs. For clarity, only the crystal of human isoform 3 is shown. Top left corner: View from the top; bottom right corner: View from the bottom. The residues in red, blue, and yellow indicate the mutations in ITPR1, 2, and 3, respectively, that have been hitherto reported in humans.

Nevertheless, the information on the ITPR molecular organization is still not sufficient for a complete mechanistic definition of its structure–function relationship [10,19]. If the central calcium conducting pore is similar to other ion channels, as suggested by the 4.7 Å structure of ITPR [16], the spatial arrangement of the cytosolic C-terminus is quite unique for ITPR; in particular, these carboxyl tails have the ability to interact with the N-terminal domains of the near subunits, suggesting a mechanism of allosteric regulation dictated by intracellular signals [16]. The feature of ITPR of being prone to modulation by nearby signals gives an idea of the complexity of the ITPR-interactome. In other words, ITPRs have the structural complexity to participate in and regulate a dense network of cellular processes. ITPRs are differently expressed in human tissues, as reported in Table 1, obtained with data retrieved from the Human Protein Atlas [20]. The effects of ITPRs have been extensively studied in preclinical models [21–29]. Here, we offer an overview of the human pathologies where ITPR alterations have a clear causative role. Moreover, we summarize the information derived from innovative studies of the disease-genome profile association, which also suggests the potential, under-investigated role of ITPR in several human pathologies.

Table 1. Protein expression levels of IP3Rs in different human tissues and organs.

Tissue	IP3R1	IP3R2	IP3R3
Cerebral cortex	XX	XX	X
Cerebellum	XX	X	XXX
Hippocampus	XX		
Caudate	XX	X	
Thyroid gland		X	X
Parathyroid gland		XXX	
Adrenal gland		XX	X
Nasopharynx		X	XX
Bronchus		XX	XX
Lung	X	X	XX
Oral mucosa		X	XX
Salivary gland		XX	
Esophagus		X	XX
Stomach	X	XX	XX
Duodenum		XX	XX
Small intestine		XX	XXX
Colon		XX	XX
Rectum		XX	XX
Liver		XX	XX
Gallbladder		XX	X
Pancreas		XX	X
Kidney	X	XXX	X
Urinary bladder		X	XX
Testis	X	XX	XXX
Epididymis	X	XX	X
Seminal vesicle	X	X	X
Prostate	X		X
Vagina			XX
Ovary		X	
Fallopian tube		XX	X
Endometrium		XX	XXX
Cervix, uterine		X	XX
Placenta		X	X
Breast	X	XXX	XX
Heart	X	XX	
Smooth muscle		XX	
Skeletal muscle		XX	
Soft tissue			
Adipose tissue		XX	
Skin		XX	XX
Appendix		XX	XX
Spleen	X		
Lymph node	X		X
Tonsil	X	X	XXX
Bone marrow		X	

X: Low, XX: Medium, XXX: High protein expression level.

2. ITPRs and Neurological Disorders

The function of ITPR has been historically assessed in the neurological field. Indeed, the first identification of P400 protein occurred in Purkinje cells and the neurological signs were the first to be studied in mice [30]. The highest number of ITPR human mutations has been identified in neurological disorders, in particular affecting the isoform 1. Indeed, ITPR1 is the most abundant isoform in the brain, regulating important functions including memory and motor coordination [31].

2.1. Spinocerebellar Ataxia

Spinocerebellar ataxia (SCA) is a term referring to a group of hereditary ataxias characterized by degenerative alterations in the part of the brain related to the movement control (cerebellum) and sometimes in the spinal cord. Van de Leemput was the first to identify the deletion of a 5′ portion of ITPR1 in British and Australian families with type 15 SCA [32]. Thereafter, the deletion of exons 1-48 of ITPR1 was identified in other populations, demonstrating that the haploinsufficiency of ITPR1 is involved in SCA15-16 [33,34]. Missense mutations in the ITPR1 gene have been later associated with SCA15: P1059L and P1074L in a Japanese family, and V494I in an Australian family [35,36].

Another form of SCA, SCA29, characterized by an early-onset motor delay, hypotonia, and gait ataxia, is one of the forms more frequently associated with ITPR1 mutations [37]. The missense mutations V1553M and N602D, identified by Huang et al. [38], are among the first mutations observed; G2547A was identified as a de novo mutation but only in one case [39]. In a cohort study on a population of 21 patients with SCA29, Zambonin et al. identified six novel mutations in the ITPR1 gene [40]: Three mutations in the IP3 binding domain (R269G, K279E, K418ins), two mutations in the transmembrane domain (G2506R, I2550T), and one in the regulatory domain (T1386M); no specific genotype–phenotype correlations were observed, but the recurrence in affected subjects suggested the pathogenic role of these mutations.

SCA has been generally associated with a loss of function of ITPR1, however, Casey et al. recently identified a gain-of-function pathogenic mutation [41], detecting a R36C missense variant in three SCA29 affected members of the same family. The resultant ITPR1 mutant displayed a higher IP3 binding affinity than the wild type counterpart, converting the pattern of intracellular calcium release from transient to sigmoidal. This evidence supports the idea that the enhancement of calcium release can contribute to SCA29 pathogenesis. In addition to missense mutations of the ITPR1 gene, a splicing variant was also associated with SCA29: The c.1207-2A-T transition was identified in exon 14 of ITPR1 in four SCA29 patients and was not found in unaffected members of the same family [42].

Notably, all the mutations described above are autosomal dominant variants; however, a missense mutation in the ITPR1 gene was similarly associated with autosomal recessive SCA: In a family with congenital SCA history, the homozygous missense mutation L1787P was identified in all affected individuals, while the heterozygous carriers were asymptomatic [43]. The ability of this mutation to alter the receptor function is only predictive, but the concerned residue is highly conserved and the transition of leucine to proline can affect the protein stability with a high probability. Moreover, missense mutations (T267M, T594I, S277I, T267R) were observed in sporadic infantile-onset SCA [44,45], in congenital ataxias (R269W, R241K, A280D, E512K) [46], and in another subtype of ataxia, ataxic cerebral palsy (S1493D) [47]; other mutations have been reported [48–51] in molecularly unassigned SCA forms (V2541A, T2490M) and in rare forms of cerebellar hypoplasia (T2552P, I2550N).

Intriguingly, there are SCA variants not directly associated with ITPR1 gene mutations, but involving genes functionally close to ITPR1 and its signaling. A good example comes from SCA2 and SCA3, where the causative mutations are alterations in ataxin-2 and -3, respectively. In both cases, the mutant forms of ATXs are able to bind ITPR1 increasing the sensitivity of the channel for IP3 and enhancing channel gating [52,53]. Of interest, ITPR1-functional alterations by ATXs seem to have a pathogenic role, as they increase the apoptosis of Purkinje cells in animal models of ataxia [54]. This evidence supports the key role of calcium homeostasis regulation by ITPR1 in these neurological disorders even if the channel function is not directly altered.

2.2. Huntington's Disease and Alzheimer's Disease

To date, genetic mutations in the ITPR1 gene with a pathological relevance in human Huntington's Disease (HD) and Alzheimer's Disease (AD) have not been detected. However, both disorders are major examples of indirect involvement of ITPR1.

In HD, the causative mutation is the poliQ expansion of Huntingtin (Htt), although the cellular and molecular mechanisms of GABAergic neurons loss are not clearly understood [55]. Of note,

the polyQ-Htt can bind ITPR1 with high affinity, sensitizing the receptor activity by IP3 [56,57]. Blocking the Htt–ITPR1 interaction in vivo was shown to regulate the abnormal calcium signaling in response to glutamate, protecting the neurons from death, and improving motor coordination [58], posing ITPR1 in a key position in HD pathophysiology and supporting the use of ITPR1-based therapies.

In AD, the pathogenic hypothesis of the beta-amyloid plaque has been extensively and historically investigated. However, in the last years, new and additional potential mechanisms have been suggested, including the dysregulation of calcium handling. In particular, ITPRs seem to have a key role in modulating calcium signals in AD [59]. Alterations in the ITPR function have been detected in cells derived from patients with AD already in 1994 [60,61]. Later, Ferreiro et al. demonstrated that antibody-aggregates are able to induce calcium release by ITPR in cortical neurons, leading to apoptosis, which was prevented by the ITPR inhibitor Xestopongin C [62].

2.3. Gillespie Syndrome

The Gillespie syndrome (GS) is a rare form of aniridia, cerebellar ataxia, and mental deficiency, described in 1965 by the American ophthalmologist Fredrick Gillespie [63]. Until 2016, its causative gene and mutations were unknown. Using a whole-exome sequencing approach, Gerber et al. identified several ITPR1 mutations in five GS-affected families [64]. In particular, the Authors detected truncating mutations in homozygous (Q1558*, R728*) or in composed heterozygous (G2102Valfs5/A2221Valfs23); the resultant truncated mutants were unable to generate a functional channel in a heterologous cell system. In the other two families, the Authors found one missense mutation (F2553L) and one deletion (K2563del) in the transmembrane domain. The latter, in addition to producing a dysfunctional channel, was able to exert a negative effect on the product derived from the wild type allele, with a dominant-negative action.

Later, next-generation sequencing approaches were used to study other GS families. The results evidenced novel missense mutations in the region of the calcium pore (N2543I), and in the regulatory domain (E2061G, E2061Q), further extending the ITPR1 mutations spectrum associated to GS [65,66].

2.4. Autism Spectrum Disorder

The Autism spectrum disorder (ASD) is a complex heterogeneous disorder with a poorly defined etiology and diagnosis criteria. Its high heritability, however, suggests a strong genetic component [67] and several genetic studies suggest that calcium homeostasis is a key determinant in its pathophysiology [68]. Recent studies demonstrate that IP_3-mediated calcium signals are significantly depressed in fibroblasts isolated from patients with ASD, identifying ITPR as a functional target in this disease [69]. These data are consistent with another study done in patients with autism in which a genetic variant of the oxytocin receptor (implicated in the etiology of ASD), causes a decline in the IP3/calcium signaling pathway in vitro [70].

2.5. Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a condition characterized by a progressive degeneration of motor neurons in the brain and spinal cord. ITPR1 and ITPR2 are the main isoforms expressed in motor neurons [71]. ITPR2 mRNA levels are elevated in peripheral blood samples of patients with ALS [72] and studies done in human cells suggest that the pharmacological inhibition of ITPR1 is a potential strategy to prevent motor neuron deterioration in ALS [73].

3. ITPRs in Autoimmune Disorders

ITPRs are important for exocrine fluid secretion including saliva, pancreatic juice, and tear secretion [74]. Interestingly, anti-ITPR antibodies have been detected in sera from patients with Sjogren's syndrome (SS) [75], a chronic autoimmune disease involving lymphocytic infiltration and loss of secretory function in salivary and lacrimal glands [76]. A recent study demonstrates that

the expression of ITPR2 and ITPR3 is significantly reduced in the salivary gland of SS patients, suggesting that deficits in ITPRs may underlie the secretory defect in SS [77].

Antibodies against ITPRs were also found in patients with rheumatoid arthritis and systemic lupus erythematosus, although the locations of the antigenic epitopes were different among the disease conditions [75].

4. ITPRs and Anhidrosis

Anhidrosis is the inability to sweat, which is responsible for heat tolerance; it is a rare disorder occurring even in the presence of morphologically normal eccrine glands, which are the main glands that respond to thermal stress with a high secretion rate. The whole-genome analysis of a family with anhidrosis and normal eccrine glands unveiled a novel missense mutation (G2498S) in ITPR type 2 [78]. This mutation occurs in the calcium pore-forming region. This association was corroborated by the observation of anhidrosis and hyperhidrosis in human pathologies linked to ITPR dysfunction; also, there was a marked reduction of sweat secretion in ITPR2$^{-/-}$ animals. Interestingly, ITPR2 inhibitors have the potential to reduce sweat production in hyperhidrosis, suggesting that ITPR2 is a potential pharmacological target in the treatment of sweat secretion conditions [78].

5. ITPRs and Cancer

Calcium has a key role in proliferation, differentiation, and migration; therefore, it is not surprising that ITPR, one of the main regulators of calcium handling, is involved in neoplastic transformation and progression [79]. Neck squamous cell carcinoma (HNSCC) was one of the first diseases connected to ITPR [80]; a whole-exome sequencing analysis of HNSCC patients revealed missense mutations affecting the ITPR3 gene, R64H, and R149L, both in the regulatory domain of the receptor [80]. Importantly, ITPR3 gene mutations were detectable only in metastatic or in recurrent tumors, but not in the respective primary tumors. This finding strongly suggests a role for ITPR3 in the metastatic process and malignant transformation, very significant if we take into account that the major problem related to HNSCC is given by recurrent metastases, which occur in more than half of the patients.

An increased expression of ITPR3 was detected in clear renal cell carcinoma compared to the unaffected part of the kidney [81]; ITPR3 silencing affected tumor growth, in vitro as well as in vivo, providing a direct proof of the involvement of this receptor in the carcinogenesis. An increased expression of ITPR3 has been also observed in cholangiocarcinoma [82] and in colorectal cancer [83]; in both cases the expression of ITPR3 correlated with the degree of neoplasia severity [82,83].

Alterations of ITPR1 and ITPR2 have been associated with the Sézary syndrome, a T-cell lymphoma with an aggressive clinical course. The analysis of gene mutations in 15 patients with the neoplastic syndrome unveiled somatic point mutations in ITPR1 including A95T in the regulatory domain and S2454F in the trans-membrane domain, and mutation in ITPR2, such as S2508L, in the trans-membrane domain [84]. These discoveries have important implications in considering ITPRs as new therapeutic targets in cancer.

6. Potential Role of ITPRs in Human Disease: Evidence from GWAS

While an evident role of ITPRs has been recognized for several human pathologies by identifying specific mutations, a potential role of this channel in other human conditions has been suggested by genome whole association studies (GWASs). Eleftherohorinou et al. have shown that a defective second messenger signaling could be involved in the predisposition to rheumatoid arthritis [85]. Specifically, alterations in ITPRs were proposed to be responsible for calcium signaling deregulations in this disease [85]. As revealed by another GWAS, the involvement of ITPR3 in the release of the macrophage migration inhibitory factor (MIF) confirmed the role of this receptor in rheumatoid arthritis [86]. In the same study, ITPR was also associated with type 1 diabetes mellitus [86], reflecting the similarity of genetic perturbations and the comparable immunological dysfunctions underlying these diseases, further corroborated by genetic analyses identifying ITPR3 as an independent risk locus in

Graves' disease [87] and allergic disorders including asthma, allergic rhinitis, atopic dermatitis [88,89], and airflow obstruction [90]. The involvement of ITPR3 in diabetes has been also confirmed by the significant recurrence of single nucleotides polymorphisms (SNPs) in the ITPR3 gene in diabetic American women [91], as well as in a Swedish nationwide study [92]. The latter study reported that a variation at rs2296336 (a SNP within ITPR3) might influence the risk of developing diabetes through an effect on alternative splicing. Moreover, rs3748079, a SNP located in the promoter region of ITPR3, has been associated with several autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, and Graves' disease in a Japanese population [93], and the variant rs999943 of ITPR3 has been linked to obesity [94]. Equally important, ITPR1 has been associated in different GWASs with diabetic kidney disease [95] and obesity-related traits [96]. Of note, a recent GWAS in a Chinese population identified *ITPR2* as a susceptibility gene for the Kashin-Beck disease, a chronic osteochondropathy characterized by cartilage degeneration [97]; in this study, a significant association between the disease and nine SNPs of *ITPR2* was described. Interestingly, the regulatory role of ITPR2 in apoptosis is a possible contributor to the Kashin-Beck disease, since excessive chondrocyte apoptosis was found to be related to cartilage lesions in affected patients [98]. Moreover, a GWAS has revealed that the ITPR signaling pathway is genetically associated with epilepsy [99], and the anti-epileptic drug levetiracetum is known to act inhibiting the release of calcium by ITPRs, highlighting the relevance of enhanced ITPRs action in epilepsy [100].

Other association studies have underlined the role of ITPRs in the cardiovascular field. The association between gene expression and dilated cardiomyopathy (DCM) has been studied by assessing the presence of CpG sites in the proximity of gene-promoters, as an index of promoter methylation and consequent downregulation of transcription [101]; using this strategy, the CpG site "cg26395694" close to the ITPR1 locus (ENSG00000150995) has been shown to be significantly associated to DCM (p-value: 2.57E-02). More in general, ITPR3-mediated pathways have been also linked to ischemic heart disease [86] and coronary artery disease [102]. ITPR3 has been associated with the risk of developing coronary artery aneurism in Taiwanese children with Kawasaki disease [103], a multisystemic vasculitis that can result in coronary artery lesions and that had been linked to aberrant calcium signaling [104]. In a case-control study involving 93 Kawasaki disease patients and 680 healthy controls, the frequency of the rs2229634 T/T genotype was significantly higher in Kawasaki disease patients with coronary artery aneurism than in patients without coronary artery aneurism [103]. The key importance of ITPRs in cardiovascular medicine is confirmed by the crucial role of ITPRs in cardiogenesis [105–107]; ergo, it may be difficult to detect mutations causing severe heart defects by using genetic analyses of patient samples postnatally, especially if considering that ITPRs have been shown to be essential in very early embryogenesis and some mutations might cause lethality in utero [108,109].

An international GWAS identified ITPR1 between the novel loci associated with blood pressure in children and adolescents [110]. Finally, in the Hispanic population, ITPR1 was associated to the pathophysiology of childhood obesity [96], while ITPR3 was linked to body mass index variants conferring a high risk of extreme obesity [94].

The GWAS demonstrated an association of ITPR1–2 with different forms of cancer, especially breast cancer [111–113]. Other studies associated the expression level of ITPR3 with the aggressiveness of different types of tumors, including colorectal carcinoma, gastric cancers [114], and head and neck squamous cell carcinoma [80]. *ITPR3* variants were also found to be implied in cervical squamous cell carcinoma [115]. Interestingly, ITPR3 appears also to actively participate in cell death in several tissues and its increased activity was demonstrated to induce apoptosis in T lymphocytes [116,117]. These findings indicate that compounds aimed at controlling the ITPR activity may be useful as a therapeutic approach for modulating immune responses in cancer.

7. Conclusions

In this systematic review, we illustrated the association of ITPRs mutations with human disorders. The mutations of ITPRs reported in humans are summarized in Table 2 and represented in Figure 1. Throughout the analysis of current literature, the involvement of ITPRs in human disease appears to be under-investigated.

Table 2. Spectrum of IP3Rs mutations identified in humans.

Mutation	IP3R Isoform	Effect on Protein	Disease	Reference
5′ deletion	IP3R1	Downregulation	SCA15	[32]
1-48 exons deletion	IP3R1	Downregulation	SCA15-16	[33,34]
P1059L	IP3R1	Missense (ND)	SCA15	[35]
P1074L	IP3R1	Missense (ND)	SCA15	[35]
V494I	IP3R1	Missense (ND)	SCA15	[36]
V1553M	IP3R1	Missense (ND)	SCA29	[38]
N602D	IP3R1	Missense (ND)	SCA29	[38]
G2547A	IP3R1	Missense (ND)	SCA29	[39]
R269G	IP3R1	Missense (ND)	SCA29	[40]
K279E	IP3R1	Missense (ND)	SCA29	[40]
G2506R	IP3R1	Missense (ND)	SCA29	[40]
I2550T	IP3R1	Missense (ND)	SCA29	[40]
T1386M	IP3R1	Missense (ND)	SCA29	[40]
R36C	IP3R1	Gain-of-function Increase of IP3 binding affinity	SCA29	[41]
c.1207-2A-T	IP3R1	Splicing variant	SCA29	[42]
L1787P	IP3R1	Protein-instability*	Autosomal-recessive SCA	[43]
T267M	IP3R1	Missense (ND)	Sporadic infantile-onset-SCA	[44,45]
T594I	IP3R1	Missense (ND)	Sporadic infantile-onset-SCA	[44,45]
S277I	IP3R1	Missense (ND)	Sporadic infantile-onset-SCA	[44,45]
T267R	IP3R1	Missense (ND)	Sporadic infantile-onset-SCA	[44,45]
R269W	IP3R1	Missense (ND)	Congenital-ataxias	[46]
R241K	IP3R1	Missense (ND)	Congenital-ataxias	[46]
A280D	IP3R1	Missense (ND)	Congenital-ataxias	[46]
E512K	IP3R1	Missense (ND)	Congenital-ataxias	[46]
S1493D	IP3R1	Missense (ND)	Ataxic-cerebral-palsy	[47]
V2541A	IP3R1	Missense (ND)	Molecular-unassigned SCA	[48]
T2490M	IP3R1	Missense (ND)	Molecular-unassigned SCA	[48]
T2552P	IP3R1	Missense (ND)	Cerebellar-hypoplasia	[50]
I2550N	IP3R1	Missense (ND)	Cerebellar-hypoplasia	[51]
Q1558	IP3R1	Truncating-protein, no functional channel	Gillespie syndrome	[64]
R728	IP3R1	Truncating-protein, no functional channel	Gillespie syndrome	[64]
F2553L	IP3R1	Missense (ND)	Gillespie syndrome	[64]
K2563 deletion	IP3R1	Dysfunctional channel with dominant negative action	Gillespie syndrome	[64]
N2543I	IP3R1	Missense (ND)	Gillespie syndrome	[65]
E2061G	IP3R1	Missense (ND)	Gillespie syndrome	[66]
E2061Q	IP3R1	Missense (ND)	Gillespie syndrome	[66]
A95T	IP3R1	Missense (ND)	Sézary syndrome	[84]
S2454F	IP3R1	Missense (ND)	Sézary syndrome	[84]
S2508L	IP3R1	Missense (ND)	Sézary syndrome	[84]
G2498S	IP3R2	Missense: dysfunctional channel *	Anhidrosis	[78]
R64H	IP3R3	Missense (ND)	HNSCC	[80]
R149L	IP3R3	Missense (ND)	HNSCC	[80]

HNSCC: Head and neck squamous cell carcinoma; ND: Not determined; SCA: Spinocerebellar ataxia; * predicted effect on protein.

The currently known contribution of the receptor to the pathogenesis of human disease is only the top of the iceberg. The information about causative genetic alterations affecting ITPRs mainly come from the neurology-related fields, cancer fields, or rare disease field, where the genetic analysis is a more common approach included in diagnostic procedures. However, in several studies of large-scale genome analysis, ITPRs recurrently emerge as a susceptibility gene for several pathological conditions. This evidence confirms that only little is known about this channel, particularly in cardiac and vascular homeostasis or metabolism. The recent findings of the physical link between ER and mitochondria, mediated by a protein complex including ITPR, suggest a potential role of the receptor in the regulation of calcium-dependent mitochondrial metabolism [118–130]. The ability of ITPR to indirectly regulate mitochondrial energetic metabolism could have a significant impact on the health and homeostasis of

the tissues strongly dependent on mitochondrial energetic production, such as cardiac and skeletal muscle. However, this aspect needs to be further explored.

The underestimated pathophysiological role of ITPR might also depend on the fact that the cellular context strongly affects the impact of ITPR alterations on calcium handling and the relative cell fate. A good example comes from a study in neuronal cells about the P1059L affecting the regulatory domain of ITPR1; this mutation increases the affinity of ITPR1 to IP3, altering the functional output of Purkinje cells, however, no differences were detected in calcium signaling between the wild type and the same mutant in B-cells [131]. The regulatory domain of ITPR is the target of several molecular partners whose expression and activity profile are different among the different cellular contexts. Therefore, the regulation around the P1059 residue of ITPR could be different—and/or of different impact—in Purkinje cells compared to other cells, such as B-cells. Nevertheless, the experiments performed in stable cell lines can alter the impact of ITPR alterations, as several adaptive pathways could affect the expression of ITPR regulatory proteins minimizing the effects of mutations. These observations encourage future studies on ITPR in the appropriate native cellular context, both in physiological and pathological conditions.

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References

1. Mikoshiba, K.; Changeux, J.P. Morphological and biochemical studies on isolated molecular and granular layers from bovine cerebellum. *Brain Res.* **1978**, *142*, 487–504. [CrossRef]
2. Mikoshiba, K.; Huchet, M.; Changeux, J.P. Biochemical and immunological studies on the P400 protein, a protein characteristic of the Purkinje cell from mouse and rat cerebellum. *Dev. Neurosci.* **1979**, *2*, 254–275. [CrossRef] [PubMed]
3. Crepel, F.; Dupont, J.L.; Gardette, R. Selective absence of calcium spikes in Purkinje cells of staggerer mutant mice in cerebellar slices maintained in vitro. *J. Physiol.* **1984**, *346*, 111–125. [CrossRef] [PubMed]
4. Maeda, N.; Niinobe, M.; Nakahira, K.; Mikoshiba, K. Purification and characterization of P400 protein, a glycoprotein characteristic of Purkinje cell, from mouse cerebellum. *J. Neurochem.* **1988**, *51*, 1724–1730. [CrossRef]
5. Furuichi, T.; Yoshikawa, S.; Miyawaki, A.; Wada, K.; Maeda, N.; Mikoshiba, K. Primary structure and functional expression of the inositol 1,4,5-trisphosphate-binding protein P400. *Nature* **1989**, *342*, 32–38. [CrossRef]
6. Furuichi, T.; Yoshikawa, S.; Mikoshiba, K. Nucleotide sequence of cDNA encoding P400 protein in the mouse cerebellum. *Nucleic Acids Res.* **1989**, *17*, 5385–5386. [CrossRef]
7. Iino, M. Biphasic Ca2+ dependence of inositol 1,4,5-trisphosphate-induced Ca release in smooth muscle cells of the guinea pig taenia caeci. *J. Gen. Physiol* **1990**, *95*, 1103–1122. [CrossRef]
8. Finch, E.A.; Turner, T.J.; Goldin, S.M. Calcium as a coagonist of inositol 1,4,5-trisphosphate-induced calcium release. *Science* **1991**, *252*, 443–446. [CrossRef]
9. Santulli, G.; Nakashima, R.; Yuan, Q.; Marks, A.R. Intracellular calcium release channels: An update. *J. Physiol.* **2017**, *595*, 3041–3051. [CrossRef]
10. Paknejad, N.; Hite, R.K. Structural basis for the regulation of inositol trisphosphate receptors by Ca(2+) and IP3. *Nat. Struct. Mol. Biol.* **2018**, *25*, 660–668. [CrossRef]
11. Belkacemi, A.; Hui, X.; Wardas, B.; Laschke, M.W.; Wissenbach, U.; Menger, M.D.; Lipp, P.; Beck, A.; Flockerzi, V. IP3 Receptor-Dependent Cytoplasmic Ca(2+) Signals Are Tightly Controlled by Cavbeta3. *Cell Rep.* **2018**, *22*, 1339–1349. [CrossRef] [PubMed]

12. Rong, Y.P.; Bultynck, G.; Aromolaran, A.S.; Zhong, F.; Parys, J.B.; De Smedt, H.; Mignery, G.A.; Roderick, HL.; Bootman, M.D.; Distelhorst, C.W. The BH4 domain of Bcl-2 inhibits ER calcium release and apoptosis by binding the regulatory and coupling domain of the IP3 receptor. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 14397–14402. [CrossRef] [PubMed]
13. Prole, D.L.; Taylor, C.W. Structure and Function of IP3 Receptors. *Cold Spring Harb Perspect Biol* **2019**, *11*. [CrossRef] [PubMed]
14. Lin, C.C.; Baek, K.; Lu, Z. Apo and InsP(3)-bound crystal structures of the ligand-binding domain of an InsP(3) receptor. *Nat. Struct Mol. Biol.* **2011**, *18*, 1172–1174. [CrossRef] [PubMed]
15. Seo, M.D.; Velamakanni, S.; Ishiyama, N.; Stathopulos, P.B.; Rossi, A.M.; Khan, S.A.; Dale, P.; Li, C.; Ames, J.B.; Ikura, M.; et al. Structural and functional conservation of key domains in InsP3 and ryanodine receptors. *Nature* **2012**, *483*, 108–112. [CrossRef]
16. Fan, G.; Baker, M.L.; Wang, Z.; Baker, M.R.; Sinyagovskiy, P.A.; Chiu, W.; Ludtke, S.J.; Serysheva, I.I. Gating machinery of InsP3R channels revealed by electron cryomicroscopy. *Nature* **2015**, *527*, 336–341. [CrossRef]
17. Chandran, A.; Chee, X.; Prole, D.L.; Rahman, T. Exploration of inositol 1,4,5-trisphosphate (IP3) regulated dynamics of N-terminal domain of IP3 receptor reveals early phase molecular events during receptor activation. *Sci. Rep.* **2019**, *9*, 2454. [CrossRef]
18. Hamada, K.; Miyatake, H.; Terauchi, A.; Mikoshiba, K. IP3-mediated gating mechanism of the IP3 receptor revealed by mutagenesis and X-ray crystallography. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 4661–4666. [CrossRef]
19. Lock, J.T.; Alzayady, K.J.; Yule, D.I.; Parker, I. All three IP3 receptor isoforms generate Ca(2+) puffs that display similar characteristics. *Sci. Signal.* **2018**, *11*, eaau0344. [CrossRef]
20. Thul, P.J.; Akesson, L.; Wiking, M.; Mahdessian, D.; Geladaki, A.; Ait Blal, H.; Alm, T.; Asplund, A.; Bjork, L.; Breckels, L.M.; et al. A subcellular map of the human proteome. *Science* **2017**, *356*, eaal3321. [CrossRef]
21. Chan, C.; Ooashi, N.; Akiyama, H.; Fukuda, T.; Inoue, M.; Matsu-Ura, T.; Shimogori, T.; Mikoshiba, K.; Kamiguchi, H. Inositol 1,4,5-Trisphosphate Receptor Type 3 Regulates Neuronal Growth Cone Sensitivity to Guidance Signals. *iScience* **2020**, *23*, 100963. [CrossRef] [PubMed]
22. Yuan, Q.; Yang, J.; Santulli, G.; Reiken, S.R.; Wronska, A.; Kim, M.M.; Osborne, B.W.; Lacampagne, A.; Yin, Y.; Marks, A.R. Maintenance of normal blood pressure is dependent on IP3R1-mediated regulation of eNOS. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 8532–8537. [CrossRef] [PubMed]
23. Perry, R.J.; Zhang, D.; Guerra, M.T.; Brill, A.L.; Goedeke, L.; Nasiri, A.R.; Rabin-Court, A.; Wang, Y.; Peng, L.; Dufour, S.; et al. Glucagon stimulates gluconeogenesis by INSP3R1-mediated hepatic lipolysis. *Nature* **2020**, *579*, 279–283. [CrossRef] [PubMed]
24. Santulli, G.; Xie, W.; Reiken, S.R.; Marks, A.R. Mitochondrial calcium overload is a key determinant in heart failure. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 11389–11394. [CrossRef]
25. Wang, Y.; Li, G.; Goode, J.; Paz, J.C.; Ouyang, K.; Screaton, R.; Fischer, W.H.; Chen, J.; Tabas, I.; Montminy, M. Inositol-1,4,5-trisphosphate receptor regulates hepatic gluconeogenesis in fasting and diabetes. *Nature* **2012**, *485*, 128–132. [CrossRef]
26. Kuchay, S.; Giorgi, C.; Simoneschi, D.; Pagan, J.; Missiroli, S.; Saraf, A.; Florens, L.; Washburn, M.P.; Collazo-Lorduy, A.; Castillo-Martin, M.; et al. PTEN counteracts FBXL2 to promote IP3R3- and Ca(2+)-mediated apoptosis limiting tumour growth. *Nature* **2017**, *546*, 554–558. [CrossRef]
27. Cheung, K.H.; Mei, L.; Mak, D.O.; Hayashi, I.; Iwatsubo, T.; Kang, D.E.; Foskett, J.K. Gain-of-function enhancement of IP3 receptor modal gating by familial Alzheimer's disease-linked presenilin mutants in human cells and mouse neurons. *Sci. Signal.* **2010**, *3*, ra22. [CrossRef]
28. Gambardella, J.; Trimarco, B.; Iaccarino, G.; Santulli, G. New Insights in Cardiac Calcium Handling and Excitation-Contraction Coupling. *Adv. Exp. Med. Biol* **2018**, *1067*, 373–385.
29. Huang, W.; Cane, M.C.; Mukherjee, R.; Szatmary, P.; Zhang, X.; Elliott, V.; Ouyang, Y.; Chvanov, M.; Latawiec, D.; Wen, L.; et al. Caffeine protects against experimental acute pancreatitis by inhibition of inositol 1,4,5-trisphosphate receptor-mediated Ca2+ release. *Gut* **2017**, *66*, 301–313. [CrossRef]
30. Maeda, N.; Niinobe, M.; Mikoshiba, K. A cerebellar Purkinje cell marker P400 protein is an inositol 1,4,5-trisphosphate (InsP3) receptor protein. Purification and characterization of InsP3 receptor complex. *EMBO J.* **1990**, *9*, 61–67. [CrossRef]

31. Hisatsune, C.; Mikoshiba, K. IP3 receptor mutations and brain diseases in human and rodents. *J. Neurochem.* **2017**, *141*, 790–807. [CrossRef] [PubMed]
32. van de Leemput, J.; Chandran, J.; Knight, M.A.; Holtzclaw, L.A.; Scholz, S.; Cookson, M.R.; Houlden, H.; Gwinn-Hardy, K.; Fung, H.C.; Lin, X.; et al. Deletion at ITPR1 underlies ataxia in mice and spinocerebellar ataxia 15 in humans. *PLoS Genet.* **2007**, *3*, e108. [CrossRef] [PubMed]
33. Marelli, C.; van de Leemput, J.; Johnson, J.O.; Tison, F.; Thauvin-Robinet, C.; Picard, F.; Tranchant, C.; Hernandez, D.G.; Huttin, B.; Boulliat, J.; et al. SCA15 due to large ITPR1 deletions in a cohort of 333 white families with dominant ataxia. *Arch. Neurol.* **2011**, *68*, 637–643. [CrossRef] [PubMed]
34. Novak, M.J.; Sweeney, M.G.; Li, A.; Treacy, C.; Chandrashekar, H.S.; Giunti, P.; Goold, R.G.; Davis, M.B.; Houlden, H.; Tabrizi, S.J. An ITPR1 gene deletion causes spinocerebellar ataxia 15/16: A genetic, clinical and radiological description. *Mov. Disord.* **2010**, *25*, 2176–2182. [CrossRef]
35. Hara, K.; Shiga, A.; Nozaki, H.; Mitsui, J.; Takahashi, Y.; Ishiguro, H.; Yomono, H.; Kurisaki, H.; Goto, J.; Ikeuchi, T.; et al. Total deletion and a missense mutation of ITPR1 in Japanese SCA15 families. *Neurology* **2008**, *71*, 547–551. [CrossRef]
36. Ganesamoorthy, D.; Bruno, D.L.; Schoumans, J.; Storey, E.; Delatycki, M.B.; Zhu, D.; Wei, M.K.; Nicholson, G.A.; McKinlay Gardner, R.J.; Slater, H.R. Development of a multiplex ligation-dependent probe amplification assay for diagnosis and estimation of the frequency of spinocerebellar ataxia type 15. *Clin. Chem.* **2009**, *55*, 1415–1418. [CrossRef]
37. Ando, H.; Hirose, M.; Mikoshiba, K. Aberrant IP3 receptor activities revealed by comprehensive analysis of pathological mutations causing spinocerebellar ataxia 29. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 12259–12264. [CrossRef]
38. Huang, L.; Chardon, J.W.; Carter, M.T.; Friend, K.L.; Dudding, T.E.; Schwartzentruber, J.; Zou, R.; Schofield, P.W.; Douglas, S.; Bulman, D.E.; et al. Missense mutations in ITPR1 cause autosomal dominant congenital nonprogressive spinocerebellar ataxia. *Orphanet. J. Rare Dis.* **2012**, *7*, 67. [CrossRef]
39. Gonzaga-Jauregui, C.; Harel, T.; Gambin, T.; Kousi, M.; Griffin, L.B.; Francescatto, L.; Ozes, B.; Karaca, E.; Jhangiani, S.N.; Bainbridge, M.N.; et al. Exome Sequence Analysis Suggests that Genetic Burden Contributes to Phenotypic Variability and Complex Neuropathy. *Cell Rep.* **2015**, *12*, 1169–1183. [CrossRef]
40. Zambonin, J.L.; Bellomo, A.; Ben-Pazi, H.; Everman, D.B.; Frazer, L.M.; Geraghty, M.T.; Harper, A.D.; Jones, J.R.; Kamien, B.; Kernohan, K.; et al. Spinocerebellar ataxia type 29 due to mutations in ITPR1: A case series and review of this emerging congenital ataxia. *Orphanet J. Rare. Dis.* **2017**, *12*, 121. [CrossRef]
41. Casey, J.P.; Hirouchi, T.; Hisatsune, C.; Lynch, B.; Murphy, R.; Dunne, A.M.; Miyamoto, A.; Ennis, S.; van der Spek, N.; O'Hici, B.; et al. A novel gain-of-function mutation in the ITPR1 suppressor domain causes spinocerebellar ataxia with altered Ca(2+) signal patterns. *J. Neurol.* **2017**, *264*, 1444–1453. [CrossRef] [PubMed]
42. Wang, L.; Hao, Y.; Yu, P.; Cao, Z.; Zhang, J.; Zhang, X.; Chen, Y.; Zhang, H.; Gu, W. Identification of a Splicing Mutation in ITPR1 via WES in a Chinese Early-Onset Spinocerebellar Ataxia Family. *Cerebellum* **2018**, *17*, 294–299. [CrossRef] [PubMed]
43. Klar, J.; Ali, Z.; Farooq, M.; Khan, K.; Wikstrom, J.; Iqbal, M.; Zulfiqar, S.; Faryal, S.; Baig, S.M.; Dahl, N. A missense variant in ITPR1 provides evidence for autosomal recessive SCA29 with asymptomatic cerebellar hypoplasia in carriers. *Eur J. Hum. Genet.* **2017**, *25*, 848–853. [CrossRef] [PubMed]
44. Sasaki, M.; Ohba, C.; Iai, M.; Hirabayashi, S.; Osaka, H.; Hiraide, T.; Saitsu, H.; Matsumoto, N. Sporadic infantile-onset spinocerebellar ataxia caused by missense mutations of the inositol 1,4,5-triphosphate receptor type 1 gene. *J. Neurol* **2015**, *262*, 1278–1284. [CrossRef]
45. Fogel, B.L.; Lee, H.; Deignan, J.L.; Strom, S.P.; Kantarci, S.; Wang, X.; Quintero-Rivera, F.; Vilain, E.; Grody, W.W.; Perlman, S.; et al. Exome sequencing in the clinical diagnosis of sporadic or familial cerebellar ataxia. *JAMA Neurol.* **2014**, *71*, 1237–1246. [CrossRef] [PubMed]
46. Barresi, S.; Niceta, M.; Alfieri, P.; Brankovic, V.; Piccini, G.; Bruselles, A.; Barone, M.R.; Cusmai, R.; Tartaglia, M.; Bertini, E.; et al. Mutations in the IRBIT domain of ITPR1 are a frequent cause of autosomal dominant nonprogressive congenital ataxia. *Clin. Genet.* **2017**, *91*, 86–91. [CrossRef]
47. Parolin Schnekenberg, R.; Perkins, E.M.; Miller, J.W.; Davies, W.I.; D'Adamo, M.C.; Pessia, M.; Fawcett, K.A.; Sims, D.; Gillard, E.; Hudspith, K.; et al. De novo point mutations in patients diagnosed with ataxic cerebral palsy. *Brain* **2015**, *138*, 1817–1832. [CrossRef]

48. Valencia, C.A.; Husami, A.; Holle, J.; Johnson, J.A.; Qian, Y.; Mathur, A.; Wei, C.; Indugula, S.R.; Zou, F.; Meng, H.; et al. Clinical Impact and Cost-Effectiveness of Whole Exome Sequencing as a Diagnostic Tool: A Pediatric Center's Experience. *Front. Pediatr.* **2015**, *3*, 67. [CrossRef]
49. Hsiao, C.T.; Liu, Y.T.; Liao, Y.C.; Hsu, T.Y.; Lee, Y.C.; Soong, B.W. Mutational analysis of ITPR1 in a Taiwanese cohort with cerebellar ataxias. *PLoS ONE* **2017**, *12*, e0187503. [CrossRef]
50. Hayashi, S.; Uehara, D.T.; Tanimoto, K.; Mizuno, S.; Chinen, Y.; Fukumura, S.; Takanashi, J.I.; Osaka, H.; Okamoto, N.; Inazawa, J. Comprehensive investigation of CASK mutations and other genetic etiologies in 41 patients with intellectual disability and microcephaly with pontine and cerebellar hypoplasia (MICPCH). *PLoS ONE* **2017**, *12*, e0181791. [CrossRef]
51. van Dijk, T.; Barth, P.; Reneman, L.; Appelhof, B.; Baas, F.; Poll-The, B.T. A de novo missense mutation in the inositol 1,4,5-triphosphate receptor type 1 gene causing severe pontine and cerebellar hypoplasia: Expanding the phenotype of ITPR1-related spinocerebellar ataxia's. *Am. J. Med. Genet. A* **2017**, *173*, 207–212. [CrossRef] [PubMed]
52. Chen, X.; Tang, T.S.; Tu, H.; Nelson, O.; Pook, M.; Hammer, R.; Nukina, N.; Bezprozvanny, I. Deranged calcium signaling and neurodegeneration in spinocerebellar ataxia type 3. *J. Neurosci.* **2008**, *28*, 12713–12724. [CrossRef] [PubMed]
53. Liu, J.; Tang, T.S.; Tu, H.; Nelson, O.; Herndon, E.; Huynh, D.P.; Pulst, S.M.; Bezprozvanny, I. Deranged calcium signaling and neurodegeneration in spinocerebellar ataxia type 2. *J. Neurosci.* **2009**, *29*, 9148–9162. [CrossRef] [PubMed]
54. Kasumu, A.W.; Hougaard, C.; Rode, F.; Jacobsen, T.A.; Sabatier, J.M.; Eriksen, B.L.; Strobaek, D.; Liang, X.; Egorova, P.; Vorontsova, D.; et al. Selective positive modulator of calcium-activated potassium channels exerts beneficial effects in a mouse model of spinocerebellar ataxia type 2. *Chem. Biol.* **2012**, *19*, 1340–1353. [CrossRef]
55. Vonsattel, J.P.; Myers, R.H.; Stevens, T.J.; Ferrante, R.J.; Bird, E.D.; Richardson, E.P. Jr. Neuropathological classification of Huntington's disease. *J. Neuropathol. Exp. Neurol.* **1985**, *44*, 559–577. [CrossRef]
56. Tang, T.S.; Tu, H.; Chan, E.Y.; Maximov, A.; Wang, Z.; Wellington, C.L.; Hayden, M.R.; Bezprozvanny, I. Huntingtin and huntingtin-associated protein 1 influence neuronal calcium signaling mediated by inositol-(1,4,5) triphosphate receptor type 1. *Neuron* **2003**, *39*, 227–239. [CrossRef]
57. Tang, T.S.; Tu, H.; Orban, P.C.; Chan, E.Y.; Hayden, M.R.; Bezprozvanny, I. HAP1 facilitates effects of mutant huntingtin on inositol 1,4,5-trisphosphate-induced Ca release in primary culture of striatal medium spiny neurons. *Eur. J. Neurosci.* **2004**, *20*, 1779–1787. [CrossRef]
58. Tang, T.S.; Guo, C.; Wang, H.; Chen, X.; Bezprozvanny, I. Neuroprotective effects of inositol 1,4,5-trisphosphate receptor C-terminal fragment in a Huntington's disease mouse model. *J. Neurosci.* **2009**, *29*, 1257–1266. [CrossRef]
59. Green, K.N.; Demuro, A.; Akbari, Y.; Hitt, B.D.; Smith, I.F.; Parker, I.; LaFerla, F.M. SERCA pump activity is physiologically regulated by presenilin and regulates amyloid beta production. *J. Cell Biol.* **2008**, *181*, 1107–1116. [CrossRef]
60. Ito, E.; Oka, K.; Etcheberrigaray, R.; Nelson, T.J.; McPhie, D.L.; Tofel-Grehl, B.; Gibson, G.E.; Alkon, D.L. Internal Ca2+ mobilization is altered in fibroblasts from patients with Alzheimer disease. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 534–538. [CrossRef]
61. Hirashima, N.; Etcheberrigaray, R.; Bergamaschi, S.; Racchi, M.; Battaini, F.; Binetti, G.; Govoni, S.; Alkon, D.L. Calcium responses in human fibroblasts: A diagnostic molecular profile for Alzheimer's disease. *Neurobiol. Aging* **1996**, *17*, 549–555. [CrossRef]
62. Ferreiro, E.; Oliveira, C.R.; Pereira, C. Involvement of endoplasmic reticulum Ca2+ release through ryanodine and inositol 1,4,5-triphosphate receptors in the neurotoxic effects induced by the amyloid-beta peptide. *J. Neurosci. Res.* **2004**, *76*, 872–880. [CrossRef] [PubMed]
63. Gillespie, F.D. Aniridia, Cerebellar Ataxia, and Oligophrenia in Siblings. *Arch. Ophthalmol.* **1965**, *73*, 338–341. [CrossRef] [PubMed]
64. Gerber, S.; Alzayady, K.J.; Burglen, L.; Bremond-Gignac, D.; Marchesin, V.; Roche, O.; Rio, M.; Funalot, B.; Calmon, R.; Durr, A.; et al. Recessive and Dominant De Novo ITPR1 Mutations Cause Gillespie Syndrome. *Am. J. Hum. Genet.* **2016**, *98*, 971–980. [CrossRef]

65. Dentici, M.L.; Barresi, S.; Nardella, M.; Bellacchio, E.; Alfieri, P.; Bruselles, A.; Pantaleoni, F.; Danieli, A.; Iarossi, G.; Cappa, M.; et al. Identification of novel and hotspot mutations in the channel domain of ITPR1 in two patients with Gillespie syndrome. *Gene* **2017**, *628*, 141–145. [CrossRef]
66. McEntagart, M.; Williamson, K.A.; Rainger, J.K.; Wheeler, A.; Seawright, A.; De Baere, E.; Verdin, H.; Bergendahl, L.T.; Quigley, A.; Rainger, J.; et al. A Restricted Repertoire of De Novo Mutations in ITPR1 Cause Gillespie Syndrome with Evidence for Dominant-Negative Effect. *Am. J. Hum. Genet.* **2016**, *98*, 981–992. [CrossRef]
67. Schmunk, G.; Gargus, J.J. Channelopathy pathogenesis in autism spectrum disorders. *Front. Genet.* **2013**, *4*, 222. [CrossRef]
68. Cross-Disorder Group of the Psychiatric Genomics, C. Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. *Lancet* **2013**, *381*, 1371–1379.
69. Schmunk, G.; Boubion, B.J.; Smith, I.F.; Parker, I.; Gargus, J.J. Shared functional defect in IP(3)R-mediated calcium signaling in diverse monogenic autism syndromes. *Transl. Psychiatry* **2015**, *5*, e643. [CrossRef]
70. Ma, W.J.; Hashii, M.; Munesue, T.; Hayashi, K.; Yagi, K.; Yamagishi, M.; Higashida, H.; Yokoyama, S. Non-synonymous single-nucleotide variations of the human oxytocin receptor gene and autism spectrum disorders: A case-control study in a Japanese population and functional analysis. *Mol. Autism* **2013**, *4*, 22. [CrossRef]
71. Van Den Bosch, L.; Verhoeven, K.; De Smedt, H.; Wuytack, F.; Missiaen, L.; Robberecht, W. Calcium handling proteins in isolated spinal motoneurons. *Life Sci.* **1999**, *65*, 1597–1606. [CrossRef]
72. van Es, M.A.; Van Vught, P.W.; Blauw, H.M.; Franke, L.; Saris, C.G.; Andersen, P.M.; Van Den Bosch, L.; de Jong, S.W.; van 't Slot, R.; Birve, A.; et al. ITPR2 as a susceptibility gene in sporadic amyotrophic lateral sclerosis: A genome-wide association study. *Lancet Neurol.* **2007**, *6*, 869–877. [CrossRef]
73. Kim, S.H.; Zhan, L.; Hanson, K.A.; Tibbetts, R.S. High-content RNAi screening identifies the Type 1 inositol triphosphate receptor as a modifier of TDP-43 localization and neurotoxicity. *Hum. Mol. Genet.* **2012**, *21*, 4845–4856. [CrossRef] [PubMed]
74. Futatsugi, A.; Nakamura, T.; Yamada, M.K.; Ebisui, E.; Nakamura, K.; Uchida, K.; Kitaguchi, T.; Takahashi-Iwanaga, H.; Noda, T.; Aruga, J.; et al. IP3 receptor types 2 and 3 mediate exocrine secretion underlying energy metabolism. *Science* **2005**, *309*, 2232–2234. [CrossRef]
75. Miyachi, K.; Iwai, M.; Asada, K.; Saito, I.; Hankins, R.; Mikoshiba, K. Inositol 1,4,5-trisphosphate receptors are autoantibody target antigens in patients with Sjogren's syndrome and other systemic rheumatic diseases. *Mod. Rheumatol.* **2007**, *17*, 137–143. [CrossRef]
76. Vivino, F.B. Sjogren's syndrome: Clinical aspects. *Clin. Immunol.* **2017**, *182*, 48–54. [CrossRef]
77. Teos, L.Y.; Zhang, Y.; Cotrim, A.P.; Swaim, W.; Won, J.H.; Ambrus, J.; Shen, L.; Bebris, L.; Grisius, M.; Jang, S.I.; et al. IP3R deficit underlies loss of salivary fluid secretion in Sjogren's Syndrome. *Sci. Rep.* **2015**, *5*, 13953. [CrossRef]
78. Klar, J.; Hisatsune, C.; Baig, S.M.; Tariq, M.; Johansson, A.C.; Rasool, M.; Malik, N.A.; Ameur, A.; Sugiura, K.; Feuk, L.; et al. Abolished InsP3R2 function inhibits sweat secretion in both humans and mice. *J. Clin. Invest.* **2014**, *124*, 4773–4780. [CrossRef]
79. Sneyers, F.; Rosa, N.; Bultynck, G. Type 3 IP3 receptors driving oncogenesis. *Cell Calcium* **2020**, *86*, 102141. [CrossRef]
80. Hedberg, M.L.; Goh, G.; Chiosea, S.I.; Bauman, J.E.; Freilino, M.L.; Zeng, Y.; Wang, L.; Diergaarde, B.B.; Gooding, W.E.; Lui, V.W.; et al. Genetic landscape of metastatic and recurrent head and neck squamous cell carcinoma. *J. Clin. Invest.* **2016**, *126*, 169–180. [CrossRef]
81. Rezuchova, I.; Hudecova, S.; Soltysova, A.; Matuskova, M.; Durinikova, E.; Chovancova, B.; Zuzcak, M.; Cihova, M.; Burikova, M.; Penesova, A.; et al. Type 3 inositol 1,4,5-trisphosphate receptor has antiapoptotic and proliferative role in cancer cells. *Cell Death Dis.* **2019**, *10*, 186. [CrossRef] [PubMed]
82. Ueasilamongkol, P.; Khamphaya, T.; Guerra, M.T.; Rodrigues, M.A.; Gomes, D.A.; Kong, Y.; Wei, W.; Jain, D.; Trampert, D.C.; Ananthanarayanan, M.; et al. Weerachayaphorn, J. Type 3 Inositol 1,4,5-Trisphosphate Receptor Is Increased and Enhances Malignant Properties in Cholangiocarcinoma. *Hepatology* **2020**, *71*, 583–599. [CrossRef] [PubMed]
83. Shibao, K.; Fiedler, M.J.; Nagata, J.; Minagawa, N.; Hirata, K.; Nakayama, Y.; Iwakiri, Y.; Nathanson, M.H.; Yamaguchi, K. The type III inositol 1,4,5-trisphosphate receptor is associated with aggressiveness of colorectal carcinoma. *Cell Calcium* **2010**, *48*, 315–323. [CrossRef] [PubMed]

84. Prasad, A.; Rabionet, R.; Espinet, B.; Zapata, L.; Puiggros, A.; Melero, C.; Puig, A.; Sarria-Trujillo, Y.; Ossowski, S.; Garcia-Muret, M.P.; et al. Identification of Gene Mutations and Fusion Genes in Patients with Sezary Syndrome. *J. Invest. Derm.* **2016**, *136*, 1490–1499. [CrossRef] [PubMed]
85. Eleftherohorinou, H.; Hoggart, C.J.; Wright, V.J.; Levin, M.; Coin, L.J. Pathway-driven gene stability selection of two rheumatoid arthritis GWAS identifies and validates new susceptibility genes in receptor mediated signalling pathways. *Hum. Mol. Genet.* **2011**, *20*, 3494–3506. [CrossRef] [PubMed]
86. Torkamani, A.; Topol, E.J.; Schork, N.J. Pathway analysis of seven common diseases assessed by genome-wide association. *Genomics* **2008**, *92*, 265–272. [CrossRef]
87. Nakabayashi, K.; Tajima, A.; Yamamoto, K.; Takahashi, A.; Hata, K.; Takashima, Y.; Koyanagi, M.; Nakaoka, H.; Akamizu, T.; Ishikawa, N.; et al. Identification of independent risk loci for Graves' disease within the MHC in the Japanese population. *J. Hum. Genet.* **2011**, *56*, 772–778. [CrossRef]
88. Ferreira, M.A.; Vonk, J.M.; Baurecht, H.; Marenholz, I.; Tian, C.; Hoffman, J.D.; Helmer, Q.; Tillander, A.; Ullemar, V.; van Dongen, J.; et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. *Nat. Genet.* **2017**, *49*, 1752–1757. [CrossRef]
89. Kichaev, G.; Bhatia, G.; Loh, P.R.; Gazal, S.; Burch, K.; Freund, M.K.; Schoech, A.; Pasaniuc, B.; Price, A.L. Leveraging Polygenic Functional Enrichment to Improve GWAS Power. *Am. J. Hum. Genet.* **2019**, *104*, 65–75. [CrossRef]
90. Wilk, J.B.; Shrine, N.R.; Loehr, L.R.; Zhao, J.H.; Manichaikul, A.; Lopez, L.M.; Smith, A.V.; Heckbert, S.R.; Smolonska, J.; Tang, W.; et al. Genome-wide association studies identify CHRNA5/3 and HTR4 in the development of airflow obstruction. *Am. J. Respir. Crit. Care Med.* **2012**, *186*, 622–632. [CrossRef]
91. Reddy, M.V.; Wang, H.; Liu, S.; Bode, B.; Reed, J.C.; Steed, R.D.; Anderson, S.W.; Steed, L.; Hopkins, D.; She, J.X. Association between type 1 diabetes and GWAS SNPs in the southeast US Caucasian population. *Genes Immun.* **2011**, *12*, 208–212. [CrossRef] [PubMed]
92. Roach, J.C.; Deutsch, K.; Li, S.; Siegel, A.F.; Bekris, L.M.; Einhaus, D.C.; Sheridan, C.M.; Glusman, G.; Hood, L.; Lernmark, A.; et al. Swedish Childhood Diabetes Study, G.; Diabetes Incidence in Sweden Study, G. Genetic mapping at 3-kilobase resolution reveals inositol 1,4,5-triphosphate receptor 3 as a risk factor for type 1 diabetes in Sweden. *Am. J. Hum. Genet.* **2006**, *79*, 614–627. [CrossRef] [PubMed]
93. Oishi, T.; Iida, A.; Otsubo, S.; Kamatani, Y.; Usami, M.; Takei, T.; Uchida, K.; Tsuchiya, K.; Saito, S.; Ohnisi, Y.; et al. A functional SNP in the NKX2.5-binding site of ITPR3 promoter is associated with susceptibility to systemic lupus erythematosus in Japanese population. *J. Hum. Genet.* **2008**, *53*, 151–162. [CrossRef]
94. Cotsapas, C.; Speliotes, E.K.; Hatoum, I.J.; Greenawalt, D.M.; Dobrin, R.; Lum, P.Y.; Suver, C.; Chudin, E.; Kemp, D.; Reitman, M.; et al. Consortium, G. Common body mass index-associated variants confer risk of extreme obesity. *Hum. Mol. Genet.* **2009**, *18*, 3502–3507. [CrossRef] [PubMed]
95. Iyengar, S.K.; Sedor, J.R.; Freedman, B.I.; Kao, W.H.; Kretzler, M.; Keller, B.J.; Abboud, H.E.; Adler, S.G.; Best, L.G.; Bowden, D.W.; et al. Diabetes, Genome-Wide Association and Trans-ethnic Meta-Analysis for Advanced Diabetic Kidney Disease: Family Investigation of Nephropathy and Diabetes (FIND). *PLoS Genet.* **2015**, *11*, e1005352. [CrossRef] [PubMed]
96. Comuzzie, A.G.; Cole, S.A.; Laston, S.L.; Voruganti, V.S.; Haack, K.; Gibbs, R.A.; Butte, N.F. Novel genetic loci identified for the pathophysiology of childhood obesity in the Hispanic population. *PLoS ONE* **2012**, *7*, e51954. [CrossRef] [PubMed]
97. Zhang, F.; Wen, Y.; Guo, X.; Zhang, Y.; Wang, X.; Yang, T.; Shen, H.; Chen, X.; Tian, Q.; Deng, H.W. Genome-wide association study identifies ITPR2 as a susceptibility gene for Kashin-Beck disease in Han Chinese. *Arthritis Rheumatol.* **2015**, *67*, 176–181. [CrossRef]
98. Wang, S.J.; Guo, X.; Zuo, H.; Zhang, Y.G.; Xu, P.; Ping, Z.G.; Zhang, Z.; Geng, D. Chondrocyte apoptosis and expression of Bcl-2, Bax, Fas, and iNOS in articular cartilage in patients with Kashin-Beck disease. *J. Rheumatol.* **2006**, *33*, 615–619.
99. Mirza, N.; Appleton, R.; Burn, S.; Carr, D.; Crooks, D.; du Plessis, D.; Duncan, R.; Farah, J.O.; Josan, V.; Miyajima, F.; et al. Identifying the biological pathways underlying human focal epilepsy: From complexity to coherence to centrality. *Hum. Mol. Genet.* **2015**, *24*, 4306–4316. [CrossRef]
100. Nagarkatti, N.; Deshpande, L.S.; DeLorenzo, R.J. Levetiracetam inhibits both ryanodine and IP3 receptor activated calcium induced calcium release in hippocampal neurons in culture. *Neurosci. Lett.* **2008**, *436*, 289–293. [CrossRef]

101. Meder, B.; Haas, J.; Sedaghat-Hamedani, F.; Kayvanpour, E.; Frese, K.; Lai, A.; Nietsch, R.; Scheiner, C.; Mester, S.; Bordalo, D.M.; et al. Epigenome-Wide Association Study Identifies Cardiac Gene Patterning and a Novel Class of Biomarkers for Heart Failure. *Circulation* **2017**, *136*, 1528–1544. [CrossRef] [PubMed]
102. Consortium, C.A.D.; Deloukas, P.; Kanoni, S.; Willenborg, C.; Farrall, M.; Assimes, T.L.; Thompson, J.R.; Ingelsson, E.; Saleheen, D.; Erdmann, J.; et al. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat. Genet.* **2013**, *45*, 25–33.
103. Huang, Y.C.; Lin, Y.J.; Chang, J.S.; Chen, S.Y.; Wan, L.; Sheu, J.J.; Lai, C.H.; Lin, C.W.; Liu, S.P.; Chen, C.P.; et al. Single nucleotide polymorphism rs2229634 in the ITPR3 gene is associated with the risk of developing coronary artery aneurysm in children with Kawasaki disease. *Int J. Immunogenet.* **2010**, *37*, 439–443. [CrossRef] [PubMed]
104. Bijnens, J.; Missiaen, L.; Bultynck, G.; Parys, J.B. A critical appraisal of the role of intracellular Ca(2+)-signaling pathways in Kawasaki disease. *Cell Calcium* **2018**, *71*, 95–103. [CrossRef]
105. Nakazawa, M.; Uchida, K.; Aramaki, M.; Kodo, K.; Yamagishi, C.; Takahashi, T.; Mikoshiba, K.; Yamagishi, H. Inositol 1,4,5-trisphosphate receptors are essential for the development of the second heart field. *J. Mol. Cell Cardiol.* **2011**, *51*, 58–66. [CrossRef]
106. Uchida, K.; Aramaki, M.; Nakazawa, M.; Yamagishi, C.; Makino, S.; Fukuda, K.; Nakamura, T.; Takahashi, T.; Mikoshiba, K.; Yamagishi, H. Gene knock-outs of inositol 1,4,5-trisphosphate receptors types 1 and 2 result in perturbation of cardiogenesis. *PLoS ONE* **2010**, *5*, e12500. [CrossRef]
107. Uchida, K.; Nakazawa, M.; Yamagishi, C.; Mikoshiba, K.; Yamagishi, H. Type 1 and 3 inositol trisphosphate receptors are required for extra-embryonic vascular development. *Dev. Biol* **2016**, *418*, 89–97. [CrossRef]
108. Miyazaki, S.; Yuzaki, M.; Nakada, K.; Shirakawa, H.; Nakanishi, S.; Nakade, S.; Mikoshiba, K. Block of Ca2+ wave and Ca2+ oscillation by antibody to the inositol 1,4,5-trisphosphate receptor in fertilized hamster eggs. *Science* **1992**, *257*, 251–255. [CrossRef]
109. Saneyoshi, T.; Kume, S.; Amasaki, Y.; Mikoshiba, K. The Wnt/calcium pathway activates NF-AT and promotes ventral cell fate in Xenopus embryos. *Nature* **2002**, *417*, 295–299. [CrossRef]
110. Parmar, P.G.; Taal, H.R.; Timpson, N.J.; Thiering, E.; Lehtimaki, T.; Marinelli, M.; Lind, P.A.; Howe, L.D.; Verwoert, G.; Aalto, V.; et al. International Genome-Wide Association Study Consortium Identifies Novel Loci Associated With Blood Pressure in Children and Adolescents. *Circ. Cardiovasc. Genet.* **2016**, *9*, 266–278. [CrossRef]
111. Michailidou, K.; Beesley, J.; Lindstrom, S.; Canisius, S.; Dennis, J.; Lush, M.J.; Maranian, M.J.; Bolla, M.K.; Wang, Q.; Shah, M.; et al. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. *Nat. Genet.* **2015**, *47*, 373–380. [CrossRef] [PubMed]
112. Michailidou, K.; Lindstrom, S.; Dennis, J.; Beesley, J.; Hui, S.; Kar, S.; Lemacon, A.; Soucy, P.; Glubb, D.; Rostamianfar, A.; et al. Association analysis identifies 65 new breast cancer risk loci. *Nature* **2017**, *551*, 92–94. [CrossRef] [PubMed]
113. Lee, J.Y.; Kim, J.; Kim, S.W.; Park, S.K.; Ahn, S.H.; Lee, M.H.; Suh, Y.J.; Noh, D.Y.; Son, B.H.; Cho, Y.U.; et al. BRCA1/2-negative, high-risk breast cancers (BRCAX) for Asian women: Genetic susceptibility loci and their potential impacts. *Sci Rep.* **2018**, *8*, 15263. [CrossRef] [PubMed]
114. Sakakura, C.; Hagiwara, A.; Fukuda, K.; Shimomura, K.; Takagi, T.; Kin, S.; Nakase, Y.; Fujiyama, J.; Mikoshiba, K.; Okazaki, Y.; et al. Possible involvement of inositol 1,4,5-trisphosphate receptor type 3 (IP3R3) in the peritoneal dissemination of gastric cancers. *Anticancer Res.* **2003**, *23*, 3691–3697. [PubMed]
115. Yang, Y.C.; Chang, T.Y.; Chen, T.C.; Lin, W.S.; Chang, S.C.; Lee, Y.J. ITPR3 gene haplotype is associated with cervical squamous cell carcinoma risk in Taiwanese women. *Oncotarget* **2017**, *8*, 10085–10090. [CrossRef] [PubMed]
116. Blackshaw, S.; Sawa, A.; Sharp, A.H.; Ross, C.A.; Snyder, S.H.; Khan, A.A. Type 3 inositol 1,4,5-trisphosphate receptor modulates cell death. *FASEB J.* **2000**, *14*, 1375–1379.
117. Mendes, C.C.; Gomes, D.A.; Thompson, M.; Souto, N.C.; Goes, T.S.; Goes, A.M.; Rodrigues, M.A.; Gomez, M.V.; Nathanson, M.H.; Leite, M.F. The type III inositol 1,4,5-trisphosphate receptor preferentially transmits apoptotic Ca2+ signals into mitochondria. *J. Biol. Chem.* **2005**, *280*, 40892–40900. [CrossRef]
118. Bartok, A.; Weaver, D.; Golenar, T.; Nichtova, Z.; Katona, M.; Bansaghi, S.; Alzayady, K.J.; Thomas, V.K.; Ando, H.; Mikoshiba, K.; et al. IP3 receptor isoforms differently regulate ER-mitochondrial contacts and local calcium transfer. *Nat. Commun.* **2019**, *10*, 3726. [CrossRef]

119. Diaz-Vegas, A.R.; Cordova, A.; Valladares, D.; Llanos, P.; Hidalgo, C.; Gherardi, G.; De Stefani, D.; Mammucari, C.; Rizzuto, R.; Contreras-Ferrat, A.; et al. Mitochondrial Calcium Increase Induced by RyR1 and IP3R Channel Activation After Membrane Depolarization Regulates Skeletal Muscle Metabolism. *Front. Physiol.* **2018**, *9*, 791. [CrossRef]
120. Carreras-Sureda, A.; Jana, F.; Urra, H.; Durand, S.; Mortenson, D.E.; Sagredo, A.; Bustos, G.; Hazari, Y.; Ramos-Fernandez, E.; Sassano, M.L.; et al. Non-canonical function of IRE1alpha determines mitochondria-associated endoplasmic reticulum composition to control calcium transfer and bioenergetics. *Nature cell biology* **2019**, *21*, 755–767. [CrossRef]
121. Cardenas, C.; Muller, M.; McNeal, A.; Lovy, A.; Jana, F.; Bustos, G.; Urra, F.; Smith, N.; Molgo, J.; Diehl, J.A.; et al. Selective Vulnerability of Cancer Cells by Inhibition of Ca(2+) Transfer from Endoplasmic Reticulum to Mitochondria. *Cell Rep.* **2016**, *14*, 2313–2324. [CrossRef] [PubMed]
122. Arruda, A.P.; Pers, B.M.; Parlakgul, G.; Guney, E.; Inouye, K.; Hotamisligil, G.S. Chronic enrichment of hepatic endoplasmic reticulum-mitochondria contact leads to mitochondrial dysfunction in obesity. *Nat. Med.* **2014**, *20*, 1427–1435. [CrossRef] [PubMed]
123. Straub, S.V.; Giovannucci, D.R.; Yule, D.I. Calcium wave propagation in pancreatic acinar cells: Functional interaction of inositol 1,4,5-trisphosphate receptors, ryanodine receptors, and mitochondria. *J. Gen. Physiol.* **2000**, *116*, 547–560. [CrossRef] [PubMed]
124. Wiel, C.; Lallet-Daher, H.; Gitenay, D.; Gras, B.; Le Calve, B.; Augert, A.; Ferrand, M.; Prevarskaya, N.; Simonnet, H.; Vindrieux, D.; et al. Endoplasmic reticulum calcium release through ITPR2 channels leads to mitochondrial calcium accumulation and senescence. *Nat. Commun.* **2014**, *5*, 3792. [CrossRef]
125. Bononi, A.; Giorgi, C.; Patergnani, S.; Larson, D.; Verbruggen, K.; Tanji, M.; Pellegrini, L.; Signorato, V.; Olivetto, F.; Pastorino, S.; et al. BAP1 regulates IP3R3-mediated Ca(2+) flux to mitochondria suppressing cell transformation. *Nature* **2017**, *546*, 549–553. [CrossRef]
126. D'Eletto, M.; Rossin, F.; Occhigrossi, L.; Farrace, M.G.; Faccenda, D.; Desai, R.; Marchi, S.; Refolo, G.; Falasca, L.; Antonioli, M.; et al. Transglutaminase Type 2 Regulates ER-Mitochondria Contact Sites by Interacting with GRP75. *Cell Rep.* **2018**, *25*, 3573–3581. [CrossRef]
127. De Stefani, D.; Bononi, A.; Romagnoli, A.; Messina, A.; De Pinto, V.; Pinton, P.; Rizzuto, R. VDAC1 selectively transfers apoptotic Ca2+ signals to mitochondria. *Cell Death Differ.* **2012**, *19*, 267–273. [CrossRef]
128. Marchi, S.; Marinello, M.; Bononi, A.; Bonora, M.; Giorgi, C.; Rimessi, A.; Pinton, P. Selective modulation of subtype III IP(3)R by Akt regulates ER Ca(2)(+) release and apoptosis. *Cell Death Dis.* **2012**, *3*, e304. [CrossRef]
129. Suman, M.; Sharpe, J.A.; Bentham, R.B.; Kotiadis, V.N.; Menegollo, M.; Pignataro, V.; Molgo, J.; Muntoni, F.; Duchen, M.R.; Pegoraro, E.; et al. Inositol trisphosphate receptor-mediated Ca2+ signalling stimulates mitochondrial function and gene expression in core myopathy patients. *Hum. Mol. Genet.* **2018**, *27*, 2367–2382. [CrossRef]
130. Hohendanner, F.; Maxwell, J.T.; Blatter, L.A. Cytosolic and nuclear calcium signaling in atrial myocytes: IP3-mediated calcium release and the role of mitochondria. *Channels (Austin)* **2015**, *9*, 129–138. [CrossRef]
131. Yamazaki, H.; Nozaki, H.; Onodera, O.; Michikawa, T.; Nishizawa, M.; Mikoshiba, K. Functional characterization of the P1059L mutation in the inositol 1,4,5-trisphosphate receptor type 1 identified in a Japanese SCA15 family. *Biochem. Biophys. Res. Commun.* **2011**, *410*, 754–758. [CrossRef] [PubMed]

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