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Review

Human diseases associated with connexin mutations☆

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ABSTRACT

Gap junctions and hemichannels comprised of connexins impact many cellular processes. Significant advances in our understanding of the functional role of these channels have been made by the identification of a host of genetic diseases caused by connexin mutations. Prominent features of connexin disorders are the inability of other connexins expressed in the same cell type to compensate for the mutated one, and the ability of connexin mutants to dominantly influence the activity of other wild-type connexins. Functional studies have begun to identify some of the underlying mechanisms whereby connexin channel mutation contributes to the disease state. Detailed mechanistic understanding of these functional differences will help to facilitate new pathophysiology driven therapies for the diverse array of connexin genetic disorders. This article is part of a Special Issue entitled: Gap Junction Proteins edited by Jean Claude Herve.

Contents

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1. Introduction

Most of the human congenital diseases were described clinically long before the underlying genetic causes were known. Patients with similar characteristics were identified and clinicians then developed diagnostic criteria based on disease features to classify different disorders. Sequencing of the human genome dramatically increased the identification of underlying causative mutations, particularly for rare disorders, and uncovered new roles for the members of many gene families in the function of multiple organ systems. This has proven true for the connexin gene family, where half of its members have currently been linked to a broad spectrum of genetic diseases. In some cases, the same phenotypic disease can be caused by mutations in three different connexin genes. In other cases, mutations within the same connexin gene can result in up to eight distinct clinical disorders. A major challenge for the field is to understand how the specific functional consequences of the gene mutations relate to the clinical similarities and differences between diseases. Here, we will summarize the currently known connexin genetic disorders and review some of the recent mechanistic advances in our understanding of how the underlying connexin mutations contribute to disease.

1.1. Connexins and intercellular communication

Gap junction channels are made from a family of proteins called connexins (Cx), and allow the direct passage of small molecules between adjacent cells, coupling them both metabolically and electrically [1,2]. Connexins have four transmembrane domains, TM1–TM4, connected by two extracellular loops, E1 and E2, which mediate docking. The N- and C-termini, and a loop connecting TM2 and TM3 are on the cytoplasmic side of the plasma membrane [3,4].

Connexins oligomerize in the ER-Golgi pathway into hemichannels (half a gap junction channel, also called a connexon) containing six connexin monomers [5,6]. The hemichannels are transported to the plasma membrane, where they can act as functional channels by themselves, or move to regions of cell contact and find a partner hemichannel from an adjacent cell to form a complete gap junction channel [3]. Unopposed hemichannels become active, or modulate their activity, under conditions of mechanical, or ischemic stress, allowing the flux of small molecules like Ca^{2+}, ATP, glutamate, or NAD^{+} across the plasma membrane, thereby eliciting signaling cascades and diverse physiological responses [7,8].

Channels formed by different connexins are functionally distinct in terms of their gating, conductance and permeability characteristics [3,9–13]. Genetic studies in mice have shown that these functional differences between connexins are important, since the loss of one isoform cannot be compensated for by replacement with another [14–16]. Virtually all cell types make more than one connexin at any given time, as illustrated by keratinocytes which express Cx26, Cx30, Cx30.3, Cx31, and Cx43 [17,18]. The co-expression of multiple connexins within a single cell diversifies the composition of the channels that can assemble. Hemichannels can be made either from a single connexin isoform (homomeric), or from more than one type (heteromeric). The formation of heteromeric hemichannels depends on the abilities of different connexins to interact; not all connexins can co-oligomerize with each other [19–22]. Docking of hemichannels to form homotypic and heterotypic gap junction channels adds an additional level of complexity. Docking compatibility is regulated by specific sequences in the E2 domain [21,23,24]. Thus, genetic mutation of a single connexin gene may influence many types of channel, which may contribute to the diverse variety of disease that can result.

2. Human disorders caused by connexin mutations

Mutations in ten different human connexin genes have been linked to twenty-eight distinct genetic diseases (Table 1). Eight of these disorders result from mutations in Cx26, and an additional six diseases are caused by mutations in Cx43. The highest number of distinct mutations has been identified in Cx32. Consequently, a great deal of the mechanistic research has focused on these connexins (see Section 3). As the sequencing technologies used to identify and link mutations to human disease continue to improve, additional connexinopathies may be identified [25].

Table 1
Genetic disorders caused by human connexin mutations.

Gene	Chromosome	Protein	Disorder(s)	OMIM
GJA1	6q22.31	Cx43	Craniometaphyseal dysplasia, autosomal recessive	218400
			Erythrokeratodermia variabilis et progressiva	133200
			Oculodentodigital dysplasia	164200
			Oculodentodigital dysplasia, autosomal recessive	257850
			Palmoplantar keratoderma with congenital alopecia	104100
			Syndactyly, type III	186100
GJA3	13q12.11	Cx46	Cataract	601885
GJA4	1p34.3	Cx37		
GJA5	1q21.2	Cx40	Atrial fibrillation, familial, 11	614049
			Atrial standstill, digenic (*GJA5*/*SCN5A*)	108770
GJA8	1q21.2	Cx50	Cataract	116200
GJA9	1p34.3	Cx59		
GJA10	6q15	Cx62		
GJB1	Xq13.1	Cx32	Charcot-Marie-Tooth neuropathy, X-linked 1	302800
GJB2	13q12.11	Cx26	Bart-Pumphrey syndrome	149200
			Deafness, autosomal dominant 3A	601544
			Deafness, autosomal recessive 1A	220290
			Hystrix-like ichthyosis with deafness	602540
			Keratitis-ichthyosis-deafness syndrome	148210
			Keratoderma, palmoplantar, with deafness	148350
			Vohwinkel syndrome	124500
			Porokeratotic eccrine ostial and dermal duct nevus	
GJB3	1p34.3	Cx31	Deafness, autosomal dominant 2B	612644
			Deafness, digenic, (*GJB2*/*GJB3*)	220290
			Erythrokeratodermia variabilis et progressiva	133200
GJB4	1p34.3	Cx30.3	Erythrokeratodermia variabilis et progressiva	133200
GJB5	1p34.3	Cx31.1		
GJB6	13q12.11	Cx30	Deafness, autosomal dominant 3B	612643
			Deafness, autosomal recessive 1B	612645
			Deafness, digenic (*GJB2*/*GJB6*)	220290
			Ectodermal dysplasia 2, Clouston type	129500
GJB7	6q14.3-q15	Cx25		
GJC1	17q21.31	Cx45		
GJC2	1q42.13	Cx47	Leukodystrophy, hypomyelinating, 2	608804
			Spastic paraplegia 44, autosomal recessive	613206
			Lymphedema, hereditary, IC	613480
GJC3	7q22.1	Cx30.2		
GJD2	15q14	Cx36		
GJD3	17q21.2	Cx31.9		
GJD4	10p11.21	Cx40.1		
GJE1	6q24.1	Cx23		

2.1. Cx26 mutations cause non-syndromic deafness, syndromic deafness with skin disease, or skin disease

Mutations in the *GJB2* gene encoding Cx26 are common in humans, with carrier frequencies in unaffected individuals reaching 2–4% in several populations [26–29]. Most of the Cx26 mutations result in non-syndromic deafness [30,31] which can be autosomal recessive (DFNB1A) or autosomal dominant (DFNA3A). Non-syndromic deafness is a partial or total loss of hearing that is not associated with other pathologies, and occurs in ~1 in 1000 newborn children. Cx26 mutations contribute to ~50% of genetic deafness and hearing loss can range

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