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DOCKopathies: A systematic review of the clinical pathologies associated with human *DOCK* pathogenic variants

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Abstract

The Dedicator of Cytokinesis (*DOCK)* family (*DOCK1–11*) of genes are essential mediators of cellular migration, growth, and fusion in a variety of cell types and tissues. Recent advances in whole genome sequencing (WGS) of patients with undiagnosed genetic disorders have identified several rare pathogenic variants in *DOCK* genes. We conducted a systematic review and performed a patient database and literature search of reported *DOCK* pathogenic variants that have been identified in association with clinical pathologies such as global developmental delay, immune cell dysfunction, muscle hypotonia, and muscle ataxia among other categories. We then categorized these pathogenic *DOCK* variants and their associated clinical phenotypes under several unique categories: developmental, cardiovascular, metabolic, cognitive, or neuromuscular. Our systematic review of *DOCK* variants aims to identify and analyze potential *DOCK*-regulated networks associated with neuromuscular diseases and other disease pathologies, which may identify novel therapeutic strategies and targets. This systematic analysis and categorization of human associated pathologies with *DOCK* pathogenic variants is the first report to the best of our

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knowledge for a unique class in this understudied gene family that has important implications in furthering personalized genomic medicine, clinical diagnoses, and improve targeted therapeutic outcomes across many clinical pathologies.

Keywords

DOCK; hypotonia; skeletal muscle; intellectual disability

Background

Dedicator of Cytokinesis (DOCK) proteins function as guanine nucleotide exchange factors (GEFs) that promote the release of GDP and GTP binding to small GTPases of the Rho protein family. The activation of these small GTPases requires the utilization of specific enzymes called guanine nucleotide exchange factors (GEFs), which serve as a molecular switch using the exchange of GDP for GTP on the Rho GTPase with the requirement of magnesium (Mg^{2+}) (Laurin & Côté, 2014). The DOCK proteins can be further classified into subfamilies (DOCKs A-D) based on evolutionary conservation of key protein-protein interaction domains. Many DOCK proteins have vital functions throughout the central nervous system and musculoskeletal system. Additionally, more recent analyses of the DOCK gene family have revealed key contributions to vascular biology, development, and health (Benson & Southgate, 2021).

Clinical and Diagnostic Implications

Currently in the literature, a number of animal models involving loss-of-function or gene-dosage studies on the *DOCK* gene family correlate to musculoskeletal, neurodegenerative disease, and neurodevelopmental disorders. For example, there are a multitude of animal studies related to understanding the role of in *Dock3* as a secondary modulator of musculoskeletal pathology and neurodegenerative disease, such as Duchenne muscular dystrophy (DMD) and Alzheimer's disease (AD) (Chen et al., 2009; Namekata et al., 2004; Reid et al., 2020; Tachi et al., 2012). Similarly, studies of human patients with *DOCK3* pathogenic variants, have been correlated with neurodevelopmental disorders, such as global developmental delay, most notably in young children (Helbig, 2017,Iwata-Otsubo, 2018). However, studies specifically on pathogenic *DOCK* variants and how they impact human disease remain limited and require further exploration. *DOCK* variants also appear with a high degree of phenotypic heterogeneity in relation to a multitude of clinical symptoms associated with a vast set of human pathologies ranging from metabolic and immune disorders to neuromuscular disorders and developmental disorders. This presents a challenge in investigating the molecular drivers and clinical pathologies caused by these rare *DOCK* gene pathogenic variants for clinicians and researchers. Therefore, this systematic review aims to provide a comprehensive analysis of human pathogenic *DOCK* variants and organize their wide range of clinical phenotypes into several unique categories, which we collectively refer to as 'DOCKopathies'.

The high degree of phenotypic heterogeneity, specifically in the clinical phenotypes observed in pathogenic *DOCK* variants is common among rare diseases, providing

challenges in diagnosis and interpretation for clinicians and researchers. This also leads to challenges in classification, particularly in the case of rare missense variants (Wu et al., 2021). The efficacy and utility of personalized genomic medicine relies on the ability to assess pathogenicity. In our systematic review, we are the first to provide a comprehensive and structured clinical and molecular analysis of all 11 *DOCK* genes as well as categorize pathogenic variants in correlation with other clinical phenotypes and outcomes.

Methods

Databases for Patient Record Variant Search Strategy

Variants of interest in *DOCK* genes were extracted from PubMed and ClinVar (Landrum et al., 2015). For our *DOCK* variant search strategy in PubMed, we used the following search terms, relating to phenotypes often presented by pathogenic variants in *DOCK* genes such as "immune", "muscle", "metabolic", and "intellectual disability". In addition we reviewed all *DOCK* variants reported in ClinVar and classified pathogenic and likely pathogenic variants by variant type and molecular consequence as classified by ClinVar. We further limited our search to the phenotypes associated with variants noted to be pathogenic or likely pathogenic associated with the terms "developmental", "cardiovascular", "nervous system", "immune system", "metabolic", and "2 or more" for those that presented with more than one category of pathophysiology. A complete summary of all DOCK genes, their chromosomal positions, and any overlapping genes are shown in Supp. Table S1. A full list of all *DOCK* pathogenic variants identified in this study are available in Supp. Table S2. These categories were determined by consulting the International Classification of Disorders-11 (ICD-11) and Human Phenotype Ontology (HPO) terms. A detailed flow diagram of these methods is available (Figures 1A and 1B).

Inclusion and exclusion criteria

Publications returned from the databases were imported into the EndNote™ reference manager, and duplicate citations were removed. Articles were included if 1) a *DOCK* variant was noted to be pathogenic or likely pathogenic for a disease or syndrome 2) if the *DOCK* variant described was associated to a developmental defect, muscle defect, neurological defect, alterations in social behavior, or other pathophysiology. Publications were excluded if the *DOCK* variant discussed had been identified in an individual where a more clearly pathogenic *DOCK* variant was seen or where the *DOCK* variant discussed was associated with only common disorders. We used the American College of Medical Genetics and Genomics (ACMG) derived ClinVar classification system to classify each variant by pathogenicity (pathogenic, likely pathogenic, benign, likely benign, risk factor, and uncertain significance), variation type (deletion, duplication, indel, insertion, single nucleotide polymorphism), and molecular consequence (frameshift, missense, nonsense, copy number gain, and copy number loss) (Richards et al., 2015). Differences in classification were studied across variants in all 11 *DOCK* genes.

Results

Organizing DOCK variants by pathogenicity, molecular consequences, and variation types

We identified and reviewed approximately 1,000 manuscripts that referenced *DOCK* variants. Our main goal was to focus on clinical data so we excluded 800 studies on exploring phenotypes in animal models for which no patient *DOCK* pathogenic variant had been identified. Following exclusions, we were left with 100 papers detailing patient cases published from 2011 to 2020 (Figure 1). In our ClinVar analysis across all 11 of the *DOCK* genes, we found that 23.40% of variants were classified as pathogenic, 2.35% were likely pathogenic, and 44.5% of were classified as variants of uncertain significance (VUS) (Figure 2A). The vast majority of variants were missense variants (Figure 2B). Approximately 62% of all variants were single nucleotide polymorphisms and approximately 20% were DNA duplications (Figure 2C).

Organizing pathogenic DOCK variants by molecular consequences

We then studied the nature, impact, and likely molecular consequences for each pathogenic or likely pathogenic *DOCK* variant across each gene. Quantification of molecular consequences is shown in Supp. Table S3. In our analysis, a wide variety of *DOCK* gene mutation types and impacts were observed, often with distinct trends in different genes (Figure 3). In *DOCK1*, pathogenic variants were reported as copy number gains or losses. In *DOCK2* variants 41.38% were copy number gains, while only a small percentage were reported as being missense and nonsense variants (3.45% and 17.24%). In *DOCK3*, pathogenic variants were identified as copy number gains and primarily as duplications. *DOCK3* pathogenic variants also presented with missense and nonsense mutations (20.00% and 10.00%, respectively). *DOCK4* and *DOCK5* pathogenic variants were mainly represented by copy number gains and losses. Frameshifts represented the largest classification of *DOCK6* variants (~33.33%). A variety of impacts of *DOCK7* patients had a large percentage were frameshifts (22.92%) and copy number losses (25.00%). *DOCK8* variants were mainly copy number losses (39.33%) while few were due to nonsense, missense, frameshift mutations or deletions (2.81%, 1.69%, 4.49%, and 12.36%). Lastly, *DOCK9*, *DOCK10*, and *DOCK11* pathogenic variant cases were mainly copy number gains or losses. However, both *DOCK9* and *DOCK10* variants among all 11 had the highest reported pathogenic mutations due to copy number gains (73.33% for *DOCK10* and 47.41% for *DOCK11*).

Organizing pathogenic DOCK variants by variation and clinical phenotype.

In DOCK1 patients, duplications (46.67%) and deletions predominated (53.33%). By contrast, the bulk of *DOCK2*, *DOCK4*, *DOCK9*, *DOCK10*, and *DOCK11* variants were duplications. Some variant types were seen predominantly in some genes. For example, *DOCK6* had a large amount of single nucleotide variants at nearly 54% of variants (Figure 4). We further analyzed each individual *DOCK* pathogenic variant and its reported pathophysiology by grouping all reported symptoms under seven categories: developmental, cardiovascular, immune system, nervous system, cognitive, metabolic, and neuromuscular or if the variant presented with multiple related pathophysiologies, it was classified as 2 or more (Figure 5). Specific pathologies attributed to each category are listed (Table 1)

and specification of each pathogenic variant per category are shown in Supp. Table S2. Additionally, a numerical summary of each *DOCK*'s variant's classifications is provided in Supp. Table S3. While many *DOCK* patient variants impacted multiple systems, the presence of pathogenic variants in nearly every *DOCK* gene resulted in a developmental phenotype (e.g. craniofacial defects, syndactyly etc.). Nearly 60% of all *DOCK* genes when impacted by a deleterious variant resulted in a developmental defect.

Notably, the plethora of developmental clinical phenotypes attributed to defects in these DOCK genes included micrognathia, intrauterine growth retardation, developmental delay, intellectual disability and a series of craniofacial defects (such as cleft palate or abnormal face shape) were associated with 10 of the 11 *DOCK* genes. *DOCK6* was reported to correlate with Adams-Oliver disease, a rare disorder characterized by defects of the scalp and abnormalities of the upper and lower limbs such as fingers, arms, toes, and legs (Shaheen et al., 2011). Many reported *DOCK3* compound heterozygous and homozygous missense variants were associated with neurodevelopmental syndromes in children including autism, attention-deficit hyperactive disorder (ADHD), global developmental delay, and neurodevelopmental disability. Interestingly, pathogenic *DOCK11* variants were associated with, more than any other *DOCK* gene, patients presenting with cognitive behavioral phenotypes including ADHD, bipolar disorder, schizophrenia, and polyphagia.

Pathogenic variants in *DOCKs 1, 2, 5, 7, 10, and 11* had commonalities in symptoms of muscle weakness such as muscle hypotonia, ataxia, or defect in coordination. This has been previously reported as associated defects in the central nervous system with patients presenting with abnormal ataxic gait and muscle hypotonia (de Silva et al., 2003; K.L. Helbig et al., 2017; Iwata-Otsubo et al., 2018; Wiltrout et al., 2019). We previously demonstrated that *DOCK3* is a dosage-sensitive regulator of pathologies in normal and DMD patient muscle, and thus identified as a novel secondary biomarker for the disease (Reid et al., 2020). Taken together with the findings presented here, this highlights the importance of appropriate regulation of this DOCK family of proteins in biological processes related to muscle, and that further exploration of these variants are needed to understand their impact in disease.

Immune system defects were associated with pathogenic *DOCK2* and *DOCK8* variants only, where distinct childhood immunological deficiencies were observed in 8.33% and 30.11% of cases. We identified case reports from several pediatric patients with compound heterozygous *DOCK2* variants and associated T- and B-cell combined immunodeficiencies lead to severe bacterial and viral infections (Dobbs et al., 2015). Similarly, *DOCK8* has important roles in dendritic cell transmigration, T-cell survival, and NK cytotoxicity. Pathogenic compound *DOCK8* heterozygous variants have also been identified in patients with combined immunodeficiency disease with elevated IgE, atopy, and recurrent viral infections (Biggs et al., 2017; Dimitrova & Freeman, 2017; Engelhardt et al., 2015). Many *DOCK* variants appeared to impact normal heart development and morphology. With the exception of *DOCK6, DOCKs1–10* reported pathogenic variant patients with phenotypes including abnormal cardiac morphology, ventricular septal defects, and malformation of the heart and blood vessels.

Commonly reported nervous system disorders were seizures, specifically *in DOCKs 1, 5, 6, 7, 8, 9, and 11*. Among these, only *DOCK2* and *DOCK11* variants were usually associated with encephalopathy, while *DOCK7* variants were associated with conditions such encephalopathy and epilepsy. We also defined a phenotypic category involving any metabolic defects in these groups. Interestingly, only patients with deleterious *DOCK6* and *DOCK7* variants correlated with pathologies pertaining to metabolic deficiencies. *DOCK6* had a reported associated case of familial hypercholesterolemia, leading to significantly elevated low-density lipoprotein (LDL). *DOCK7* was reported in a patient with hypobetalipoproteinemia (FHBL), a disorder that impairs the absorption and transport of lipids. Interestingly, introns of both *DOCK6* and *DOCK7* appear to modulate the expression of Angiopoietin-like (*ANGPTL*s) genes located on the opposite DNA strand of the introns of the *DOCK6* and *DOCK7* genes which have important roles in the trafficking and metabolism of lipids (Quagliarini, 2012). This highlights their novel role and the identification of these rare *DOCK* variants may play in the pathophysiology of known clinical disease, as well as their identification leading to the development of potential therapeutic targets.

Future Prospects

DOCK family members have been shown to modulate or activate downstream effectors such as Rho GTPases like RAC1, RHOA, WAVE/WASF1, and N-WASP. Many of these pathways are involved in the rearrangement of the actin cytoskeleton, metabolism, and cell migration. They are strongly expressed in the brain and spinal cord (Côté & Vuori, 2002; Makihara et al., 2018). Recently, deleterious variants in these genes have been identified as pathogenic in relation to a variety of disorders with pathologies ranging from cognitive, to developmental, to cardiovascular effects. *DOCK* variants have been identified in pathologies related to cognitive function in terms of behavior such as attention deficit hyperactive disorder (ADHD), autism, or global developmental delay (GDD) (K. L. Helbig et al., 2017; Iwata-Otsubo et al., 2018). Other pathogenic *DOCK* variants are identified in relation to developmental disorders, including craniofacial defects, and neurological defects such as ataxia and hypotonia. In this systematic review, we sought to analyze, interpret, and classify these *DOCK* variants by molecular consequence, mutation type, and phenotypic association. In doing so we have generated a comprehensive review of clinical outcomes related to pathogenic *DOCK* variants. Our findings highlight the more than 3,000 *DOCK* pathogenic variants identified in patients to date span copy number gains and losses, frameshifts, missense and nonsense variants, and other types of small and large deletions and duplications. Copy number gains predominate, ranging as the cause of disease from as low as 10% of variants to nearly 67% in particular *DOCK* genes. This number is undoubtedly impacted by biases related to the testing methodology and initial discovery of causation for this type of variant.

The over-representation of larger duplications or deletions can present a challenge in therapeutic solutions if using gene editing technologies such as clustered regularly interspaced short palindromic repeats (CRISPR) or exon-skipping drugs to restore multi-exon deletions (Aartsma-Rus et al., 2009; Aartsma-Rus et al., 2012; Adikusuma et al., 2017; Adkin et al., 2012; Akcakaya et al., 2018). As previously noted, nearly 60% of

cases involving pathogenic *DOCK* variants had a developmental phenotype. This can be a challenge to therapeutic approaches, as our findings indicate that there may be limitations in effectiveness for specific DOCK-associated developmental pathologies, as well as complications in assuring that therapeutic approaches can cross the blood brain barrier to achieve efficacy. Drug targeting involving Rho GTPases, such as RAC, may be a more attractive alternative for variants with large multi-exon deletions, where gene editing technologies would be unusable (Guo et al., 2019).

Our results further noted that patients with deleterious variants in several of these *DOCK* genes present with cognitive behavioral phenotypes such as ADHD and global developmental delay (K. L. Helbig et al., 2017; Iwata-Otsubo et al., 2018). Indeed, we found that nearly every pathogenic DOCK subclass presented with a cognitive behavioral phenotype. Nearly 5% of pathogenic variants across all genes resulted in a neuromuscular disorder such as ataxia or hypotonia. Patients with *DOCK6* and *DOCK7* pathogenic variants present with metabolic phenotypes (Table 1 and Figure 5). Both *DOCK6* and *DOCK7* contain domains involved in activation of the Rho GTPase, RAC1, which is responsible for a variety of metabolic pathways such as insulin signaling and glucose processing. Additionally, both DOCKs have been shown to regulate Angiopoietin-like proteins (ANGPTLs) a gene family that has been identified as important regulators of metabolic disorders, specifically ANGPTL8 in introns 18 and 19 of *DOCK6* and Angiopoietin-like 3 (ANGPTL3) within the intron of *DOCK7* (Quagliarini, 2012). This highlights the importance of identifying novel gene networks and rare pathogenic variants in order to find novel and effective potential therapeutic targets.

Investigating these broad spectrum of *DOCK* pathogenic variants and associated pathologies holds potential for development of therapeutic targets to ameliorate disease and symptoms through the intersection of experimental and computational modeling. This analysis can be used to evaluate the plausibility for pathogenic disease and enhance therapeutic potential to treat known diseases. The investigation of rare, pathogenic *DOCK* variants may allow for evaluation of their impact at structural and functional levels on protein function and stability, which may be able to predict *DOCK* variant risk to human health or how they may worsen clinical outcomes (Petrosino et al., 2021). Defining commonalities among *DOCK* variants causing disease in DOCKopathies, will aid in identifying plausible therapeutic approaches such as oligo-mediated gene exon-skipping and CRISPR-mediated gene editing to restore DOCK protein function and yield treatments for this subset of patients. These strategies are being applied successfully to enhance quality of life and outcomes for patients with other rare genetic disorders and their families.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement:

All data is full available in the aforementioned databases.

Web resources:

https://www.ncbi.nlm.nih.gov/clinvar/

https://pubmed.ncbi.nlm.nih.gov/

https://hpo.jax.org/app/

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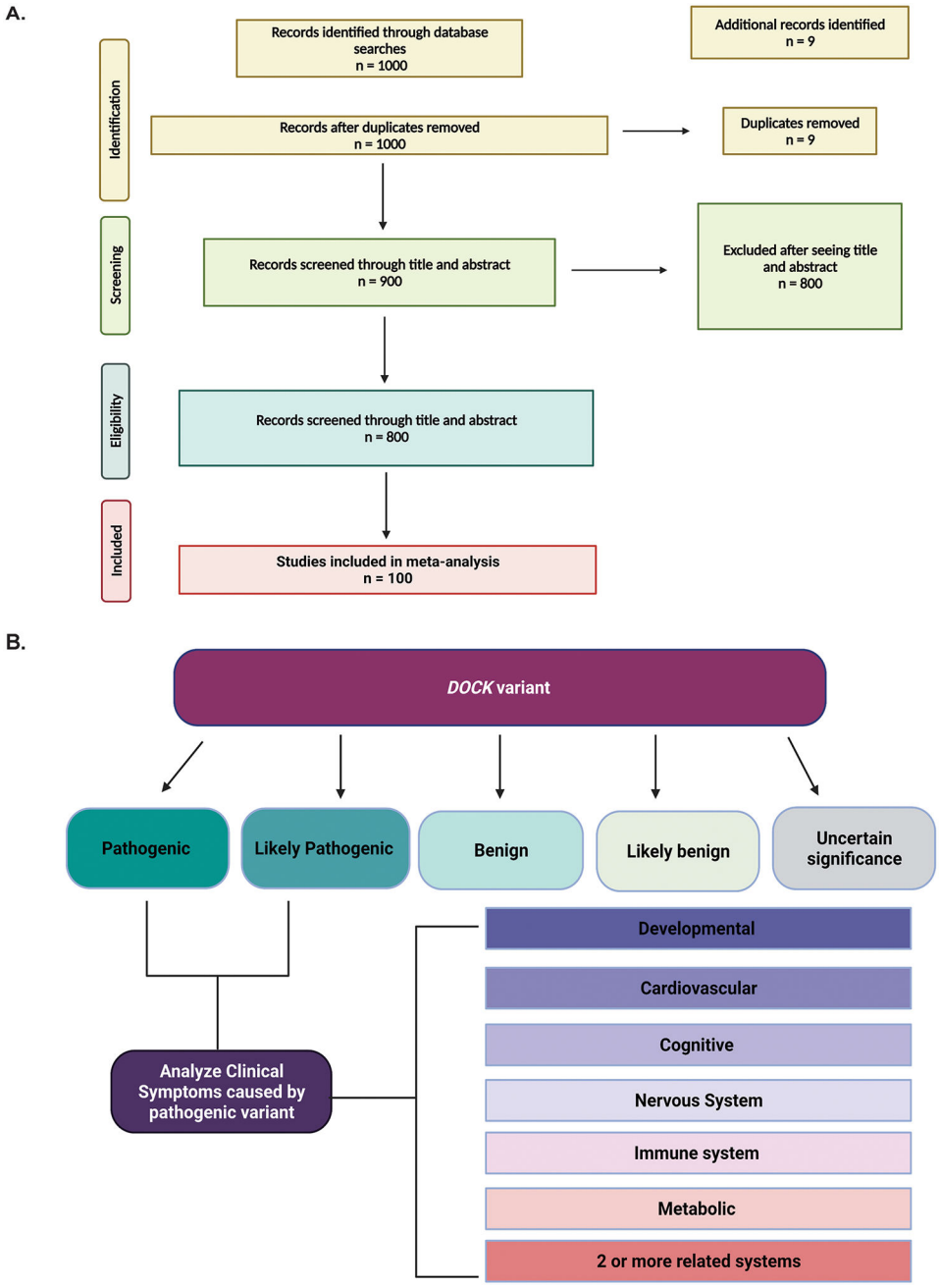

Figure 1: Summary of Methodology.

Meta-analysis was conducted using two databases, PubMed and ClinVar. Initial inquiry began with PubMed (A) in which we reviewed 1000 available primary articles on *DOCK* variants. We continued our search analyzing reported variants in ClinVar (B) in which we sorted each variant as reported by ClinVar in their respective categories.

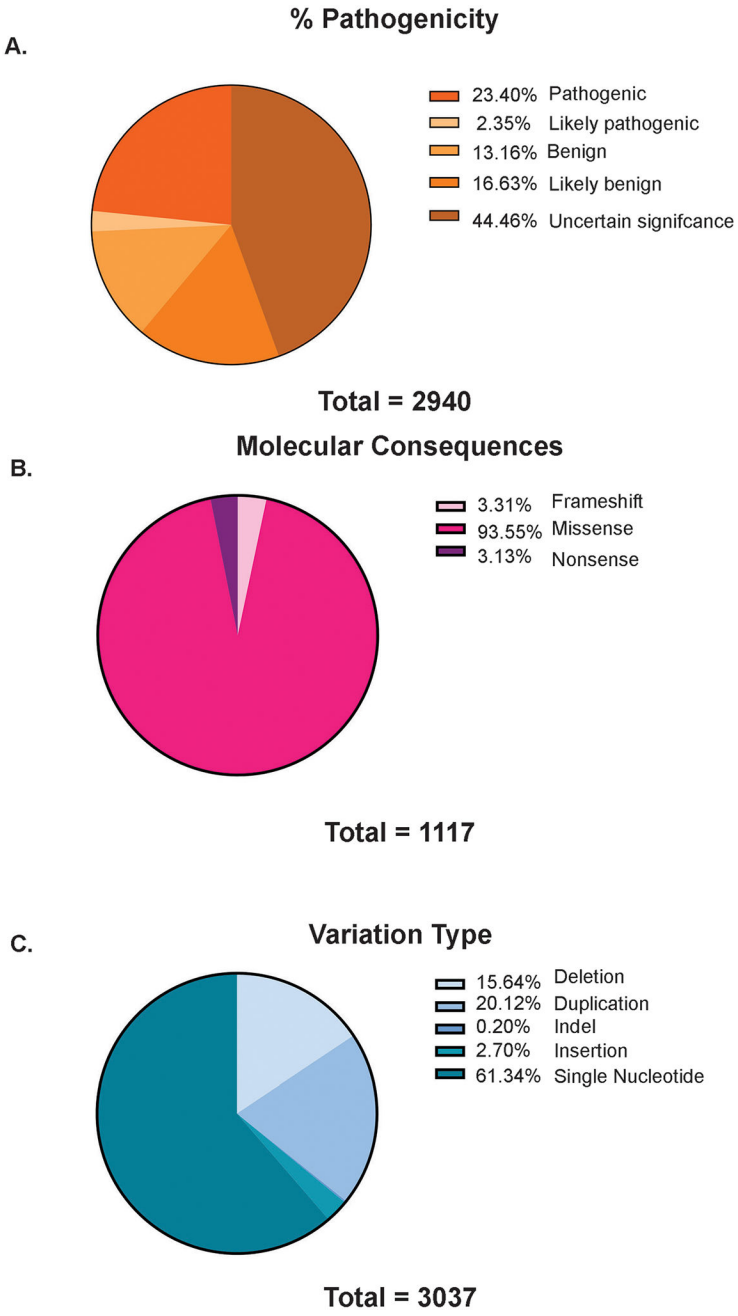

Figure 2: All *DOCK* variants identified and sorted in ClinVar.

Comprehensive analysis at all *DOCK* variants identified on ClinVar. We sorted variants for their percentage (%) pathogenicity (A), by molecular consequence as either frameshift, nonsense, or missense (B) and sorted by variant type, as either deletion, duplication, indel, insertion, or single nucleotide (C).

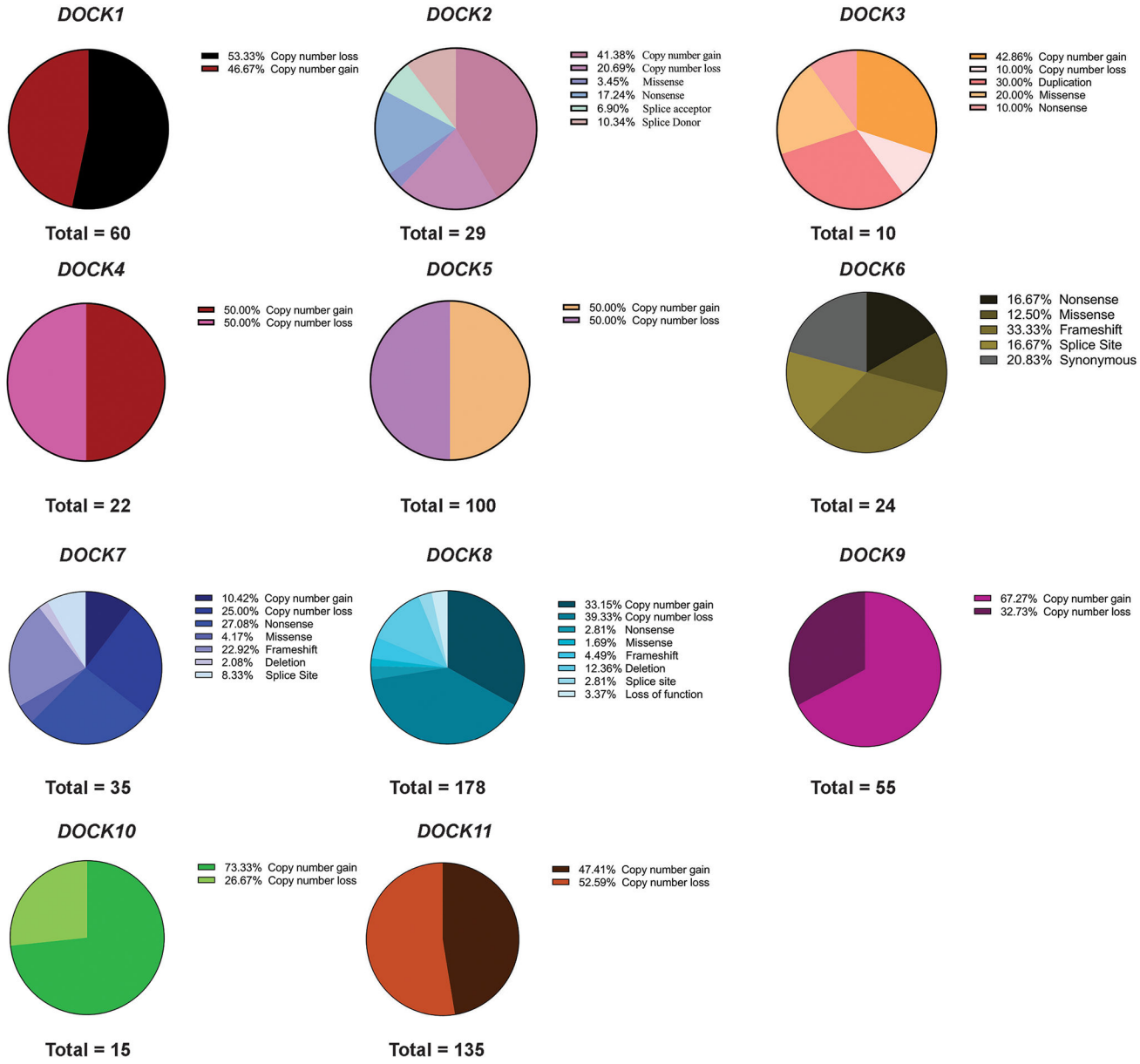

Figure 3: *DOCK* variant molecular consequences.

Each pathogenic *DOCK* variant for each subclass (1–11) were analyzed by molecular consequence as reported by ClinVar.

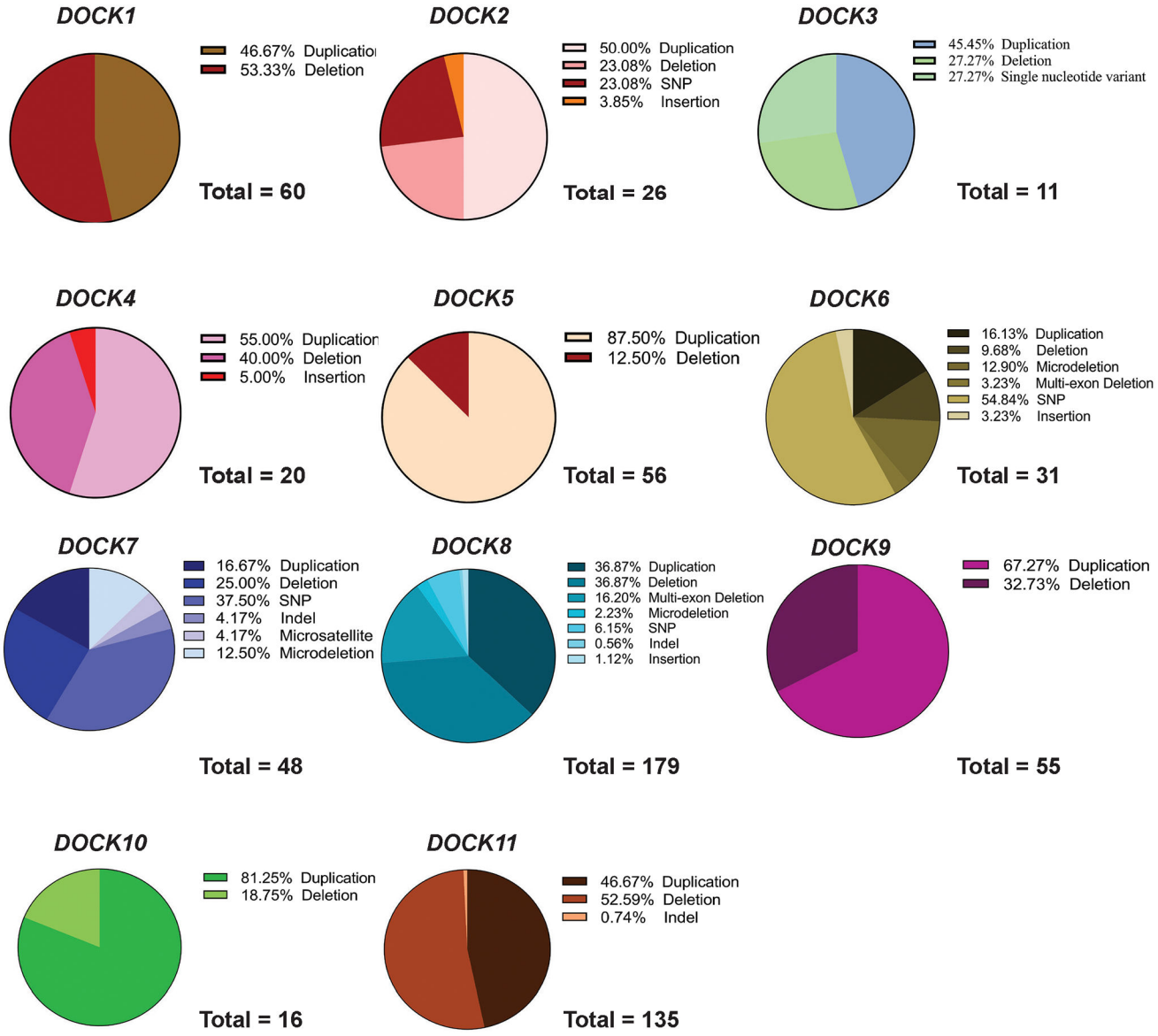

Figure 4: *DOCK* Mutation Type.

Each pathogenic *DOCK* variant for each subclass (1–11) was analyzed by variant type, either duplication, deletion, indel, insertion etc. as reported by ClinVar.

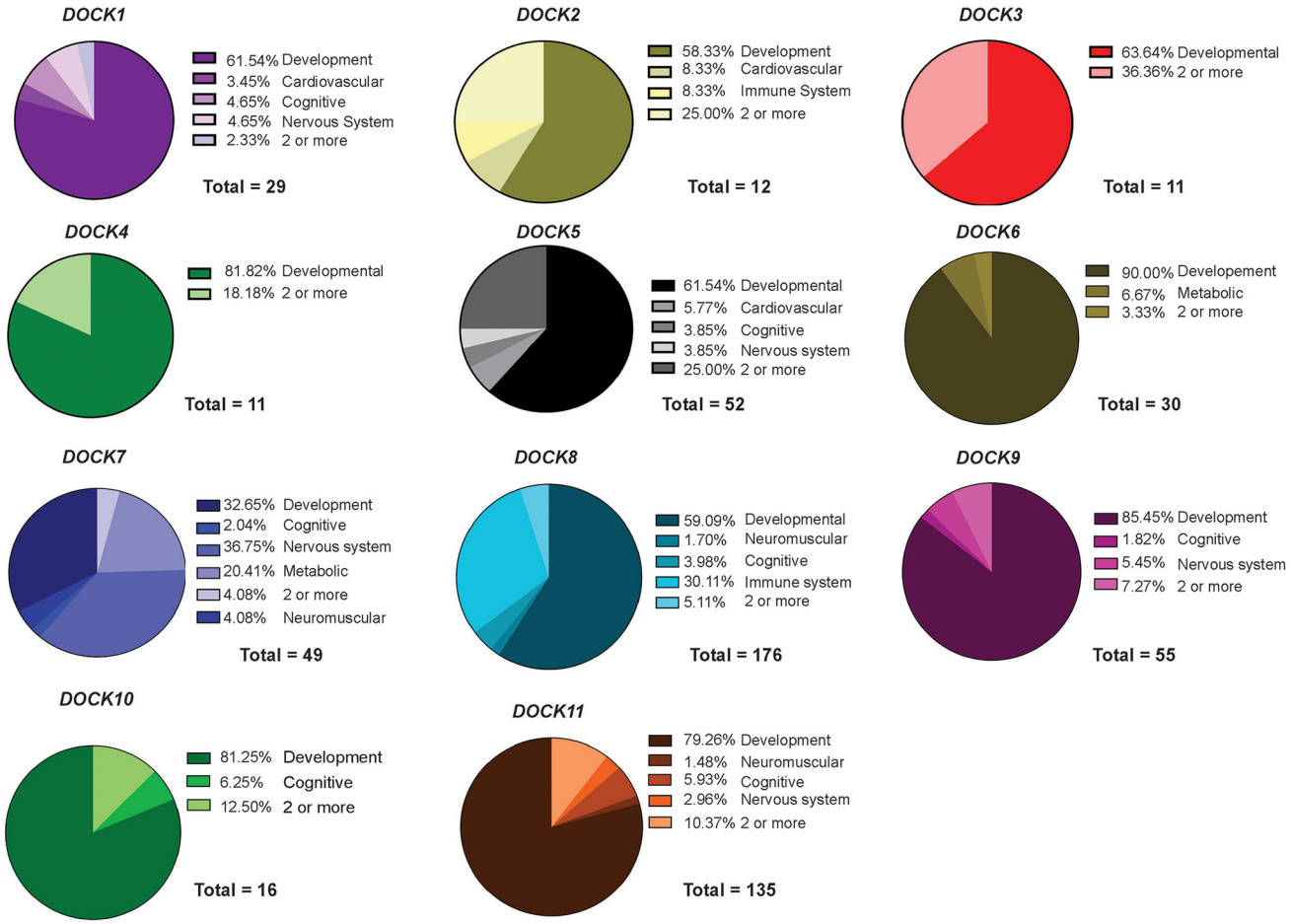

Figure 5: Clinical Symptoms of *DOCK* pathogenic variants.

DOCK pathogenic variants were identified on ClinVar and were collectively categorized by several classifications: ‘Developmental’, ‘Cardiovascular’, ‘Cognitive’, ‘Metabolic’, ‘Nervous system’, and if there were multiple conditions associated with each category they were sorted as ‘2 or more’.

Table 1.
Clinical Presentations of Pathogenic *DOCK* Variants.

Clinical symptoms as reported by ClinVar for each pathogenic *DOCK* variant and their respective categorization in Figure 5 are listed.

Development	
Symptom	**DOCKs Presenting**
abnormal facial shape	DOCK1, DOCK2, DOCK3, DOCK4, DOCK5, DOCK7, DOCK8, DOCK9, DOCK10, DOCK11
abnormality of limb and bone morphology	DOCK5
abnormality of the ear	DOCK1, DOCK2, DOCK4, DOCK5, DOCK7, DOCK8, DOCK9, DOCK10, DOCK11
abnormality of the skull	DOCK4
abnormality of the vertebrae	DOCK5, DOCK11
Adams-Oliver Syndrome	DOCK6
Adams-Oliver Syndrome 2	DOCK6
agenesis of the corpus callosum	DOCK1, DOCK5, DOCK8, DOCK9
ambiguous genitalia	DOCK4, DOCK8, DOCK11
Arnold-Chiari malformations	DOCK5, DOCK8
bilateral hyperplasia of choroid plexus	DOCK8
bilateral single tranverse palmar creases	DOCK5, DOCK9
blepharophimosis	DOCK8, DOCK11
camptodactyly	DOCK2
cerebellar hypoplasia	DOCK8
cerebral white matter hypoplasia	DOCK1
cleft palate	DOCK1, DOCK2, DOCK4, DOCK5, DOCK8, DOCK9, DOCK10, DOCK11
clinodactyly	DOCK8, DOCK10
coarse facial features	DOCK2, DOCK10
coloboma	DOCK2, DOCK5, DOCK8, DOCK9, DOCK10
craniosynostosis	DOCK2, DOCK8, DOCK11
cryptorchidism	DOCK1, DOCK5, DOCK8, DOCK10,
Dandy-Walker malformation	DOCK9
delayed fine motor development	DOCK1, DOCK2, DOCK5, DOCK8, DOCK9, DOCK11
delayed gross motor development	DOCK1, DOCK2, DOCK4, DOCK5, DOCK8, DOCK9
delayed speech and language development	DOCK1, DOCK4, DOCK5, DOCK8, DOCK9, DOCK10, DOCK11
developmental delay	DOCK1, DOCK2, DOCK3, DOCK4, DOCK5, DOCK6, DOCK7, DOCK8, DOCK9, DOCK10, DOCK11
distal urethral duplication	DOCK1
dolichocephaly	DOCK2, DOCK8
dysmorphic features	DOCK2, DOCK3
esotropia	DOCK9
failure to thrive	DOCK5, DOCK6, DOCK8, DOCK9, DOCK10, DOCK11
fetal cystic hygroma	DOCK1

gastroesophageal reflux	DOCK2
genu recurvatum	DOCK8
global developmental delay	DOCK1, DOCK2, DOCK3, DOCK4, DOCK5, DOCK6, DOCK7, DOCK8, DOCK9, DOCK11
gonadal dysgenesis	DOCK11
holoprosencephaly	DOCK2, DOCK9, DOCK11
hydrocephaly	DOCK8
hydroureter	DOCK5
hypertelorism	DOCK9, DOCK11
hypospadias	DOCK10
hypotelorism	DOCK1
increased nuchal translucency	DOCK5, DOCK8, DOCK11
intrauterine growth retardation	DOCK1, DOCK2, DOCK3, DOCK4, DOCK5, DOCK7, DOCK8, DOCK9, DOCK10, DOCK11
macrocephaly	DOCK2, DOCK8, DOCK9, DOCK11
microcephaly	DOCK1, DOCK5, DOCK8, DOCK9, DOCK11
microglossia	DOCK2
micrognathia	DOCK1, DOCK2, DOCK3, DOCK4, DOCK5, DOCK7, DOCK8, DOCK9, DOCK10, DOCK11
micropenis	DOCK1, DOCK8
multiple congenital anomalies	DOCK1
nevus flammeus	DOCK9
omphalocele	DOCK8, DOCK9
Pierre-Robin sequence	DOCK2
platybasia	DOCK5
polydactyly	DOCK1, DOCK2, DOCK4, DOCK5, DOCK7, DOCK8, DOCK9, DOCK10, DOCK11
ptosis	DOCK11
csoliosis	DOCK2, DOCK5, DOCK8, DOCK10, DOCK11
short stature	DOCK2, DOCK3, DOCK4, DOCK5, DOCK7, DOCK8, DOCK9, DOCK10, DOCK11
smooth philtrum	DOCK1, DOCK9
strabismus	DOCK1
syndactyly	DOCK1, DOCK2, DOCK3, DOCK4, DOCK5, DOCK7, DOCK8, DOCK9, DOCK10, DOCK11
talipes equinovarus	DOCK8, DOCK9, DOCK11
tapered fingers	DOCK5
tracheomalachia	DOCK8
trigonocephaly	DOCK8
urinary tract malformations	DOCK7
ventriculomegaly	DOCK8, DOCK9,
vitiligo	DOCK5
wide nasal bridge	DOCK5, DOCK8, DOCK9, DOCK10, DOCK11
Cardiovascular	

Symptom	DOCKs Presenting
abnormality of cardiac morphology	DOCK5, DOCK8, DOCK11
abnormality of the fetal cardiovascular system	DOCK5
aortic valve stenosis	DOCK11
atria septal defect	DOCK4, DOCK5, DOCK8, DOCK9, DOCK10, DOCK11
bicuspid aortic valve	DOCK8
coarctation of the aorta	DOCK8, DOCK9, DOCK10
esophageal atresia	DOCK8, DOCK11
heart murmur	DOCK8
hypertrophic cardiomyopathy	DOCK11
hypoplastic aortic arch	DOCK9
hypoplastic left heart	DOCK5, DOCK8, DOCK11
mitral valve prolapse	DOCK1
obsolete malformation of the heart and great vessels	DOCK1, DOCK2, DOCK4, DOCK5, DOCK7, DOCK8, DOCK9, DOCK10, DOCK11
patent ductus arteriosis	DOCK1, DOCK2, DOCK8, DOCK11
pericardial effusion	DOCK5
pulmonic stenosis	DOCK8
right bundle branch block	DOCK1
supraventricular tachycardia	DOCK2
tetrology of Fallot	DOCK8, DOCK9, DOCK10
ventricular septal defect	DOCK1, DOCK2, DOCK3, DOCK4, DOCK5, DOCK7, DOCK8, DOCK9, DOCK10, DOCK11
Cognitive Behavioral	
Symptom	**DOCKs Presenting**
ADHD	DOCK1, DOCK8
aggressive behavior	DOCK1
anxiety	DOCK8
autistic behavior	DOCK1, DOCK5, DOCK8, DOCK10, DOCK11
bipolar affective disorder	DOCK9, DOCK11
intellectual disability	DOCK1, DOCK2, DOCK5, DOCK7, DOCK8, DOCK9, DOCK10, DOCK11
learning disability	DOCK5, DOCK8, DOCK11
polyphagia	DOCK11
schizophrenia	DOCK11
Nervous System Disorder	
Symptom	**DOCKs Presenting**
bilateral sensorineural hearing impairment	DOCK9, DOCK11
cerebral palsy	DOCK1,
encephalopathy	DOCK2, DOCK11
epileptic encephalopathy	DOCK7
seizures	DOCK1, DOCK5, DOCK6, DOCK8, DOCK9, DOCK11

Immune System	
Symptom	**DOCKs Presenting**
hyper-IgE recurrent infection sydrome, autosomal recessive	DOCK8
hypogammaglobulinemia	DOCK10
immunodeficiency	DOCK2, DOCK8
Metabolic	
Symptom	**DOCKs Presenting**
familial hypercholesterolemia 1	DOCK6
hypobetalipoproteinemia, familial, 2	DOCK7
Neuromuscular	
Symptom	**DOCKs Presenting**
ataxia	DOCK1, DOCK3
dystonia	DOCK1,
flexion contracture	DOCK4, DOCK5, DOCK10
gait ataxia	DOCK1,
gait disturbance	DOCK8, DOCK11
generalized amyotrophy	DOCK5
hypotonia	DOCK3, DOCK4, DOCK5, DOCK7, DOCK8, DOCK9, DOCK10, DOCK11
iIncoordination	DOCK5, DOCK11
involuntary movements	DOCK4
severe neonatal hypotonia in males	DOCK5
spasticity	DOCK2, DOCK8, DOCK11
torticollis	DOCK5