# Supplementary data

# A disorder clinically resembling cystic fibrosis caused by biallelic variants in the *AGR2* gene

## Methods

### Exome Sequencing (ES)

ES was performed as previously described [1]. In short, Twist Human Core Exome Plus, the Nextera Rapid Capture Exome Kit (Illumina, San Diego, CA) or the SureSelect Human All Exon kit (Agilent, Santa Clara, CA) were used for the enrichment, and a HiSeq4000 (Illumina) instrument for the sequencing with the 150 paired-end protocol to yield at least 20x coverage of depth for >98% of the target region. An in-house bioinformatics pipeline, including read alignment to human genome reference (hg19), variant calling (single nucleotide and small deletion/insertion variants) and variant annotation with publicly available databases, was used [1].

All provided clinical data, family history, consanguinity, disease onset/course, and available test results were considered. The type of variant and frequency in public databases, such as gnomAD, ExAc, as well as disease-centered databases (HGMD and CentoMD®), were considered.

### Sanger Validation and Co-Segregation Analysis

The *AGR2* exons containing the variants were amplified (primers available upon request) and Sanger-sequenced in both forward and reverse direction on a 3730xl sequencer (Thermo Fisher Scientific, Waltham, MA). The copy number variant (deletion) was confirmed by quantitative PCR assays (qPCR), targeting several exons within the copy number variant and

1-2 additional fragments outside the deletion. Products were run in a LightCycler 480 II (Roche).

Ceramide26 Quantification in Dried Blood Spots

C26 Ceramide species were quantified in dried blood spots extract using a method previously described[2], using Multiple reaction monitoring- mass spectrometry.

Perforations of 3.2 mm in diameter were cut using a DBS puncher (Perkin Elmer LAS, Germany) and placed in deep well plate (Thermo Scientific, Germany). 50 µL extraction solution (DMSO: water, 1:1) and 100 µL internal standards solution in ethanol were added on top. Plate was sealed and placed in an incubator (Heidolph, Germany) for 30 minutes at 37 °C under agitation at 700 rpm. After incubation, the plate was sonicated for 10 minutes at maximum power and then the liquid was transferred to an AcroPrep Filter Plate with PTFE membrane (PALL, Germany) placed on a 96 well V-shape bottom plate (VWR, Germany). The samples were filtrated by centrifugation for 5 minutes at 3500 rpm in a Hermle Z300 plate centrifuge (Hermle Labortehnik, Germany). The clear extract was measured using LC/MRM-MS on a Waters Acquity UPLC (Waters, UK) coupled with an ABSciex 5500 TripleQuad mass spectrometer (ABSciex, Germany). Chromatographic run was performed on a C8, 3 µm, Column, 50 × 2.1 mm (ACE, ACE, Germany) using a flow rate of 0.9 mL/min preheated at 60 °C. The analytes were eluted using a gradient with type 6 curve from 40% A (50 mM formic acid in water) to 100% B (50 mM formic acid in acetone: acetonitrile vol. 1:1). Multiple reaction monitoring- mass spectrometry (MRM-MS) analyses were performed in positive ion mode using the following parameters: CUR gas 10 psi, IS voltage 5 kV, CAD 8 psi, cone temperature 200 °C, GS1 45 psi, GS2 60 psi, EP 10 V.

Clinical Description of the Affected Individuals

*Family 1, individuals IV-2, IV-1 and IV-4*

The index patient (IV-2) is a female born to healthy consanguineous parents from Oman (Figure 1A). The family history is positive, with three relatives having a similar phenotype of recurrent respiratory infections and failure to thrive. One affected sibling deceased with a similar phenotype. The index has presented recurrent lower respiratory tract infections, wheezing, and failure to thrive since infancy, which caused regular hospital admissions. A chest X-ray showed hyperinflated lungs and mild peribronchial wall thickening. A high-resolution computed tomography (HRCT) showed mild bilateral bronchiectasis and mosaic pattern. Repeated thorax CT scan showed diffuse mosaic pattern, bronchiectasis, and hilar lymphadenopathy. Given the clinical suspicions of cystic fibrosis, a sweat chloride test was performed, which was normal. Exome sequencing, indicated for diagnostic purposes, did not identify any relevant variant among known disease genes. Then, a second analysis was performed including genes not yet associated to a human phenotype.

Individual IV-1 (cousin). She has been suffering from recurrent respiratory infections and wheezy episodes since the neonatal period, with multiple hospital admissions. Between these episodes she has been having daily wet coughing, as well as poor weight gain. Immunological work up and cystic fibrosis investigations were all normal. A HRCT of the thorax at the age of nine months showed features suggestive of mild basal bronchiectasis and of bronchiolitis obliterans. A bronchoscopy, echocardiography, and a barium swallow test were normal. A tuberculosis workup was negative. A lung biopsy at the age of two years showed mild peri bronchial lymphocytic inflammation with no evidence of lung fibrosis. Currently, she has poor weight gain, and suffers from chronic coughing, and exertional dyspnea with intermittent wheezing. The most recent HRCT showed a diffuse mosaic pattern with bronchial wall thickening, mild bronchiectasis, fibrotic bands, mild collapse, few pulmonary nodules, and hilar lymphadenopathy. Detailed studies: Microbiology surveillance (sputum and throat swap) were negatives (no culture growth). Bronchoalveolar lavage: sample of whitish color, semi-mucoid, by microscopy groups of reactive respiratory epithelial cells were observed, mucus

with admixture of neutrophil and lymphocytes, no fungal elements are demonstrated by GMS, the results are consistent with an inflammatory process. No bacterial growth. Lung biopsy: The sections show four profiles of lung covered by pleura. The pleura is edematous and shows prominent vessels. There are some adhesions. The lung parenchyma appears normal with slight over distension of the air spaces, there is no subpleural fibrosis. However, at the resection margin the parenchyma is collapsed. No cartilage containing bronchi are present within the specimen. There is a focal lymphocytic and histiocytic infiltrate around bronchioles that is nodular. There is no diffuse inflammatory cell infiltrate in the interstitial or air spaces. PAS staining is negative. There are collections of foamy cells in the lumen of one of the bronchioles. There is no alveolar proteinosis and no type 2 pneumocyte hyperplasia is seen. The appearances are not specific in these sections. There is some mild peri bronchial lymphocytic infiltration and the presence of foamy cells within the lumina suggest possible mild bronchial obstruction. The appearances do not suggest surfactant protein deficiency and immunostaining for surfactant protein B is normal. The vasculature appears unremarkable on elastic staining. Conclusion: Mild peri bronchial lymphocytic inflammation.

Individual IV-4 (cousin). Since the neonatal period, she has presented with persistent wet coughing, recurrent wheezing episodes, and dyspnea. She had multiple admissions due to persistent lower respiratory infections. A physical examination revealed no dysmorphism, no clubbing, bilateral crackles at chest auscultation, and delayed motor development with right hemiplegia. A head CT scan displayed a left basal ganglia and left thalamus smaller than the right side, indicating atrophic changes (Wallerian degeneration) probably due to an old ischemic insult. Currently, she suffers from intermittent productive coughing. After completing an extensive rehabilitation plan for the hemiplegia, she can walk and run relatively normal. Her HRCT has showed segmental areas of mosaic perfusion with bronchial wall thickening, mild bronchial dilatation, and tiny nodules with tree-in-bud appearance. Mediastinal and hilar lymphadenopathy were seen. The bronchoscopy was normal with no

airway anomalies noted, but a clear secretion was observed all over the airways. Bronchoalveolar lavage: three smears of bronchial lavage examined, they show numerous macrophages and mixed inflammatory cell infiltrate. Few reactive bronchial epithelial cells were seen, and no malignant cells noted. Microbiology: no growth. Microbiology surveillance by sputum culture and throat swap was negative. Laboratory investigations including targeted genetic analysis excluded primary immunodeficiency, cystic fibrosis, primary ciliary dyskinesia, aspiration syndrome and mitochondrial cytopathy.

*Family 2, individual III-1*

The index is a male born to consanguineous parents, who are from Syrian origin. His birth weight was 3.2 kg. The patient had history of passing frequent loose stools since birth, for which his formula milk has been changed several times with no improvement. He was admitted to the hospital for acute gastroenteritis and pneumonia during the neonatal period. The patient was again readmitted after three weeks from discharge with history of still passing frequent loose watery stools that was greenish in color. In addition, the patient had also history of chronic cough that was productive in nature, associated with vomiting whitish sputum. To rule out cystic fibrosis, sweat chloride test was performed that came normal (27 mmol/L) and repeated (33 mmol/L).

The patient was again readmitted a few months later with the impression of pneumonia and receive a course of antibiotics, upper GI study was requested and was found to have severe GERD. The patient had frequent follow ups with the respiratory and GI team and was been managed as a case of hyperactive airway disease, cow’s milk allergy and severe GERD.

Upon examination patient was noticed to have subtle dysmorphic features, prominent forehead, upslanting palpebral fissures, and thin upper lips.

*Family 3, individual IV-1*

The index is a male born to consanguineous asymptomatic parents from Iraq. His brother died during infancy after a long-term hospitalization due to chronic diarrhea, vomiting, and renal failure. He has a similarly affected cousin (deceased, Figure 1A). The index presented soon after birth with severe vomiting and diarrhea leading to admission to the intensive care unit.

*Family 4, individual II-1*

The index is a female born to healthy consanguineous parents from Syrian origin. She was born at full term with normal birth weight (3 kg). It was noticed that she presented with persistent coughing and she was admitted with the impression of severe pneumonia and treated with a course of antibiotics. During early childhood, she was examined for speech delay and was found to have sensorineural hearing impairment. Currently, the patient is still suffering from recurrent respiratory infections and a chronic productive cough, which regularly requires hospital admission. Exome sequencing detected a homozygous likely pathogenic variant in the *SLC26A4* gene with the diagnosis of autosomal recessive deafness type 4, which explains the hearing impairment. However, this finding did not clarify the cause of the respiratory symptoms.

According to the parents, the patient is still having recurrent lower respiratory infections requiring hospital admissions and chronic cough that is productive in nature despite being on prophylactic antibiotics weekly.

*Family 5, individual II-1*

The index is a deceased female. Her consanguineous parents are from Egypt. The index's younger brother is similarly affected (Figure 1). The index presented with recurrent lower respiratory tract infection, interstitial lung disease, hepatosplenomegaly, hypotonia, and global developmental delay. The recurrent lower respiratory tract infections started at the age of eight months, leading to prolonged hospitalizations in the intensive care unit. She also had

right-sided heart failure, which was thought to be secondary to the respiratory condition. A brain MRI and EMG (upper and lower limbs) were normal. The thorax CT scan showed bilateral patchy ground glass haze and right lower lobe patchy consolidation with trans bronchial spread and intervening areas of hyperventilation. In addition, progressive diffuse reticulo - nodular infiltrates and bilateral atelectatic bands were detected. An echocardiography showed right ventricular and right atrial dilatation, with tricuspid regurgitation and severe pulmonary hypertension. An ultrasound of the abdomen revealed an enlarged liver with homogenous echogenic parenchymal texture. The immunological profile was normal, apart from a slightly low percentage of CD4+ T-cells. A sweat chloride test was normal. Her brother has presented with recurrent lower respiratory infections that led to multiple hospitalizations. He has had normal neurodevelopment with slightly delayed motor milestones. A physical examination revealed pectus carinatum and hepatomegaly of approximately 3 cm. A CT scan of the thorax showed well defined patch areas of ground glass appearance and scattered consolidations in both lungs.

*Family 6, individual III-1*

The index is a male born to asymptomatic consanguineous parents, who are residents of Oman, with no family history of similar clinical picture. He presented with recurrent lower respiratory tract infections since infancy. Later, he had recurrent episodes of ear infection and otorrhea, which did not respond well to antibiotic therapy. He also had recurrent upper tract respiratory infections and coughing. A nasal ciliary brush study was done with motile cilia seen under light microscopy. Unfortunately, the sample was not adequate for electron microscopy. His bronchoscopy test was completely normal. Bronchoalveolar lavage (BAL) culture was positive for pseudomonas. The BAL cytology showed cellular fluid composed of bronchial epithelial cells and alveolar macrophages. Strands of thick mucus were seen in a

background containing many neutrophils. No alveolar cast, micro-organisms or atypical cells were detected. However, scattered lipid laden macrophages were observed.

*Family 7, individuals IV-2 and IV-3*

The index is a male from Syria, born to consanguineous parents. He was born after an uneventful pregnancy and delivery (at term). The index presented soon after birth with chronic diarrhea, poor weight gain, and mild hepatomegaly. During early childhood, he had recurrent otorrhea and middle ear infections, which did not respond well to antibiotic therapy. He also had upper tract respiratory infections and dried cough. He was evaluated by the immunology team (upon clinical suspicion of primary immunodeficiency); however, all lab tests were normal. A chest CT scan showed randomly distributed bilateral airspace consolidations, some are nodular with no cavitation, and mild bronchial wall thickening. Multiple enlarged mediastinal and hilar lymph nodes, mild bilateral pleural effusion with no pericardial effusion or pneumothorax. Microbiology cultures detected pseudomonas in both airway secretion and ear discharge. Nasal brush examination revealed rare epithelial cells with cilia, with 9+2 normal configuration. Ultrastructural electron microcopy examination was not possible due to a suboptimal quality of the sample. The liver shows diffuse low density could be due to fatty infiltration. Abdominal ultrasound showed a mildly enlarged liver with homogeneous parenchyma and no focal lesion. Screening for several infectious diseases had negative results as well (tuberculosis, CMV, EBV, HIV). Other test performed included sweat chloride, pancreatic elastase, Alpha 1 antitrypsin, and nasal brush test (also normal). Laboratory testing resulted normal excluded intestinal parasite infections. Multiple blood, urine and stool cultures were negative as well.

There are other similarly affected relatives. A male sibling deceased during infancy with a clinical picture of chronic diarrhea and progressive respiratory disease. A cousin deceased

with a progressive respiratory disease. A female sibling (IV-3) is affected with chronic diarrhea and recurrent lower tract respiratory infections (Figure 1A).

*Family 8, individual II-1*

The index is a male, presenting since early childhood with recurrent low tract respiratory infections and persistent rhinorrhea. He is adopted and history of his biological relatives is not available. He had persistent vomiting and dysphagia with hard food. Esophagogastroduodenoscopy with histopathology study, and echo were normal. CT chest showed bronchiectatic changes and persistent segmental collapse in the left lower lobe. Also, persistent direct hyperbilirubinemia with mild hepatomegaly, were detected with other liver function tests within normal limits. Furthermore, he is followed by a sleep therapist for obstructive sleep apnea likely due to upper airway obstruction.

Immunological workup revealed normal results including immunoglobulin, lymphocyte subset analysis and oxidative burst test. Ciliary abnormalities were detected in 34% of the examined cilia, the abnormalities were related to missing central doubles, triplets instead of central doubles with missing dynein arms (inner and/or outer) at peripheral doubles, and duplication of central doublets with missing dynein arms (inner and/or outer) at peripheral doublets (Supplementary figure). Although suggestive of primary ciliary dyskinesia, in most patients with a true ciliary defect most cilia are abnormal [3]. Additional testing included throat swab cultures (Escherichia coli in 3 different occasions).

*Family 9, individual II-4*

The index is a male, born to consanguineous parents from Pakistan. During the neonatal period, he presented respiratory distress. A few weeks later, he developed respiratory distress followed by inter costal and sub costal recessions and lethargy. He was admitted to the hospital for more than a month with pneumonia. Later, he presented loose stools and frequent

episodes of dehydration. He persisted to have course of respiratory symptoms and marked weight loss due to diarrheal episodes. His neurodevelopment is normal.

**Supplementary Table 1.** Clinical characteristics of patients identified with ***AGR2*** homozygous variants (NM_006408.3)

| | **Fam. 1, IV-1** (2427168) | **Fam. 1, IV-2** (2427168) | **Fam.1, IV-4** (2427168) | **Fam. 2, III-1 (**2438720) | **Fam. 3, IV-1** (2399903) | **Fam. 4, II-1 (**2337168) | **Fam. 5, II-1 (**2151518) | **Fam. 5, II-2 (**2151518) | **Fam. 6, III-1** (2451078) | **Family 7** (2518771) | **Family 7** (2518771) | **Family 8** (2508357) | **Family 9** (2534592) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *AGR2* variant - NM_006408.3 | c.211C>A p.Pro71Thr exon 4 | c.211C>A p.Pro71Thr exon 4 | c.211C>A p.Pro71Thr exon 4 | c.349C>T p.His117Tyr exon 6 | c.349C>T p.His117Tyr exon 6 | c.349C>T p.His117Tyr exon 6 | c.330+1G>T intron 5 | c.330+1G>T intron 5 | Large deletion (exon 1- 7 chr7:16834456-16918247) | c.349C>T p.His117Tyr exon 6 | c.349C>T p.His117Tyr exon 6 | c.330+1del intron 5 | c.428G>A p.Gly143Glu (exon 7) |
| **Current life stage** | Childhood | Childhood | Childhood | Childhood | Infancy | Childhood | Deceased | Childhood | Childhood | Childhood | Early childhood | Childhood | Early childhood |
| **Sex** | Female | Female | Female | Male | Male | Female | Female | Male | Male | Male | Female | Male | Male |
| **Consanguinity** | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Unknown | Yes |
| **Geographical region** | Oman | Oman | Oman | Bahrain (of Syrian origin) | Iraq | Bahrain (of Syrian origin) | Egypt | Egypt | Oman | Saudi Arabia | Saudi Arabia | Saudi Arabia | Pakistan |
| **Family history** | Yes (cousins) | Yes (cousins and sibling) | Yes (cousins) | No | Yes (deceased brother and cousin) | No | Yes (brother) | Yes (deceased sister) | No | Yes (siblings and deceased cousin) | Yes (siblings and deceased cousin) | N/A (adopted) | No |
| **Age at onset** | 2 weeks | 6 months | 1 week | At birth | 2 days | 1 year | 8 months | 10 days | 6 months | At birth | At birth | 2 years | 3 days |
| **Failure to thrive** | Yes, weight below 5$^{th}$ percentile | Yes, weight below 5$^{th}$ percentile, height at 10$^{th}$ percentile | Yes, weight below 5$^{th}$ percentile | Yes | Yes, weight, height and OFC below 5$^{th}$ percentile | Yes, weight 5$^{th}$ percentile | Yes | Yes | Yes | Low weight (weight <3$^{rd}$ percentile, height 25$^{th}$ percentile) | Low weight (weight <3$^{rd}$ percentile, height 10$^{th}$-25$^{th}$ percentile) | Yes | Yes, height and weight below 5$^{th}$ percentile |
| **Dysmorphism** | None | None | None | Prominent forehead, Upslanting palpebral fissures, Thin upper lips | None | None | None | None | None | None | None | None | None |
| **Motor development** | Appropriate for age | Appropriate for age | Delayed motor development with right hemiplegia | Appropriate for age | Mild motor delay | Appropriate for age | Appropriate for age | Mild motor delay | Appropriate for age | Appropriate for age | Appropriate for age | Appropriate for age | Appropriate for age |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Mental development** | Appropriate for age | Appropriate for age | Appropriate for age | Appropriate for age | Appropriate for age | Appropriate for age | Speech delay | Appropriate for age | Appropriate for age | Appropriate for age | Appropriate for age | Appropriate for age | Appropriate for age |
| **Neurological abnormalities** | None reported | None reported | Hemiparesis, Paucity in the movement of the right side of the body | None reported | None reported | None reported | Global developmental delay, Hypotonia | None reported | None reported | None reported | None reported | None reported | None reported |
| **Recurrent lower respiratory tract infections** | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **Pulmonary abnormalities** | Chronic coughing, Exertional dyspnea, Basal crackles, Bronchial wall thickening, Hilar lymphadenopathy Mild bronchiectasis, fibrotic bands | Chronic coughing, Bilateral crackles, Mild bronchiectasis Hilar lymphadenopathy | Chronic coughing, Recurrent wheezing episodes, Dyspnea, Bilateral crackles, Bronchial wall thickening, Mediastinal and hilar lymphadenopathy | Chronic coughing, Pneumonia, Hyperactive airway disease | Mild respiratory tract infections | Chronic coughing, Severe pneumonia | Interstitial lung disease | Recurrent wheezing episodes, Patch areas of ground glass appearance and scattered consolidations in both lungs | Bronchiectasis, Chronic coughing | Chronic cough, Pleural effusion, hilar lymphadenopathy Bronchiectasis | Chronic cough, hilar lymphadenopathy | Bronchiectasis, Persistent segmental collapse in the left lower lobe, Chronic productive cough | Collapse/consolidation in segments of both lungs. Subsegmental atelectasis. Small bilateral axillary lymph nodes |
| **Immunological abnormalities** | None reported | None reported | None reported | None reported | None reported (see test results) | None reported | Slightly low percentage of CD4+ T-cells | None reported | None reported | Leukocytosis, Lymphocytosis | None reported | None reported | Leucocytosis |
| **Gastroenteric abnormalities** | None | None | None | Acute gastroenteritis, Vomiting, Severe gastroesophageal reflux, Chronic diarrhea | Chronic diarrhea, Episodic vomiting, lethargy | None | Hepatomegaly | Choking, vomiting and chronic diarrhea, Hepatomegaly | None | Chronic diarrhea (improved after 2 y), hepatomegaly | Chronic diarrhea | Persistent vomiting, hepatomegaly and persistent cholestasis | Chronic diarrhea, abdominal distention with prominent veins, no visceromegaly |
| **Cardiovascular abnormalities** | None, Echocardiogram - normal | Mitral valve prolapse, Mitral regurgitation | None | None | None | None | Right sided heart failure, Right ventricular and right atrial dilatation, | None | None | None | None | None | None, Echocardiogram - normal |

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| | | | | | | | Tricuspid regurgitation, Severe pulmonary hypertension | | | | | | |
| **Other tests results** | Sweat chloride test, Bronchoscopy, Imunological profile – all normal | Heterozygous VUS in CFTR, c.4091C>T, p.Ala1364Val Sweat chloride test - normal | Bronchoscopy - normal | Sweat chloride test, Immunological profile - normal | Decreased T-cell count with low CD4+/CD8+ ratio, low B-cell count and slightly increased NK-cell count | Sweat chloride test, Immunological profile – normal Hom LP SLC26A4, NM_000441.1:c.1339_1340delinsTCT | Sweat chloride test - normal | Liver function test - normal | Bronchoalveolar lavage culture - positive for pseudomonas | Sweat chloride test, Pancreatic elastase, Nasal brush test (light microscopy) – all normal Het pathogenic variant *GAA* NM_000152.3:c.-32-13T>G | Hom pathogenic variant *GAA* NM_000152.3:c.-32-13T>G | Lymphocyte subset analysis, Immunoglobulins, and oxidative burst test – all normal. EM nasal brush - ciliary abnormalities in 34% of examined cilia | Sweat chloride test, Pancreatic elastase – normal |
| **Clinical suspicion** | Cystic fibrosis, Primary ciliary dyskinesia | Cystic fibrosis, Primary ciliary dyskinesia, Primary Immunodeficiency | Primary immunodeficiency, Cystic fibrosis, Primary ciliary dyskinesia, Aspiration syndrome and Mitochondrial cytopathy | Cystic fibrosis | Type 1 distal, renal tubular acidosis, congenital enteropathies, chloride losing diarrhea, Primary Immunodeficiency | Cystic fibrosis | Cystic fibrosis, Niemann-Pick disease type 2 | Cystic fibrosis | Cystic fibrosis, Primary ciliary dyskinesia | Primary ciliary dyskinesia, Cystic fibrosis Primary immunodeficiency | Cystic fibrosis, Primary immunodeficiency, Malabsorption | Primary ciliary dyskinesia | Cystic fibrosis, Primary immunodeficiency |
| **Other** | | | | Cow's milk allergy | | Otitis media. Sensorineural hearing impairment (cochlear implant) | | | Rhinorrhea | Chronic suppurative otitis media, Mediastinal lymphadenopathy | Recurrent otitis media | Sino-nasal polyposis by CT, obstructive sleep apnoea, Rhinitis, Recurrent otitis media | |

Footnote: Infancy: < 1 year of age, early childhood: >1-5 years, childhood >5-14 years. OFC: Occipitofrontal circumference

**Supplementary table 2**. Rare homozygous coding variants remaining as candidates in family 1, 2, 3, 4, 5, 7, 8, and 9. Homozygous variants detected in other samples in our or external data repositories (healthy individuals) were excluded.

| Chr | Genomic coordinate | *Gene* | Reference seq: nucleotide change | Reference seq.: protein change | Variant type | dbSNP | OMIM | PyloP | Cadd raw | PopFreq Max |
|---|---|---|---|---|---|---|---|---|---|---|
| **Family 1 - 2427168** | | | | | | | | | | |
| chr10 | 96117097 | *NOC3L* | NM_022451.10:c.351-10delT | | Splice region variant & intron variant | rs753480410 | 610769 | | | 0.0002 |
| chr12 | 66707785 | *HELB* | NM_033647.4:c.1700C>T | NM_033647.4:p.Ser567Leu | Missense | rs149157869 | 614539 | 0.388 | 0.34089 | 0.0053 |
| chr2 | 85661241 | *SH2D6* | NM_201594.2:c.41+7G>A | | Splice region variant & intron variant | | | | | |
| chr2 | 97820417 | *ANKRD36* | NM_001164315.1:c.1199T>C | NM_001164315.1:p.Leu400Pro | Missense | - | - | -0.113 | 0.77015 | |
| chr2 | 234394541 | *USP40* | NM_018218.2:c.3313G>A | NM_018218.2:p.Ala1105Thr | Missense | rs374106216 | 610570 | 0.548 | -1.37204 | 0.0003 |
| chr20 | 7895021 | *HAO1* | NM_017545.2:c.335C>A | NM_017545.2:p.Thr112Asn | Missense | rs377526496 | 605023 | 9.513 | 4.90385 | 0.001 |
| **chr7** | **16840820** | ***AGR2*** | **NM_006408.4:c.211C>A** | **NM_006408.3:p.Pro71Thr** | **Missense** | **-** | **606358** | **9.276** | **6.14466** | |
| chr9 | 141015116 | *CACNA1B* | NM_000718.3:c.6272C>T | NM_000718.3:p.Pro2091Leu | Missense | rs746163681 | 601012 [Neurodevelopmental disorder with seizures and nonepileptic hyperkinetic movements] | 0.285 | 1.59689 | 0.0015 |
| **Family 2 -2438720** | | | | | | | | | | |
| chr10 | 82298271 | *SH2D4B* | NM_207372.2:c.184G>A | NM_207372.2:p.Ala62Thr | Missense | rs749601744 | | 4.15 | 1.70092 | 0.0003 |
| chr15 | 23686239 | *GOLGA6L2* | NM_001304388.1:c.1382_1383insCGAGGAGGAGAAGATGCGGGA | NM_001304388.1:p.Arg460_Glu461insAspGluGluGluLysMetArg | Disruptive inframe insertion | | | | | |
| chr17 | 6928019 | *BCL6B* | ENST00000293805.5:c.720_731delCAGCAGCAGCAG | ENST00000293805.5:p.Ser241_Ser244del | Disruptive inframe deletion | | 608992 | | | |
| chr17 | 7918378 | *GUCY2D* | NM_000180.3:c.2769+9T>G | | Splice region variant& intron variant | rs771741738 | 600179 [?Choroidal dystrophy, central areolar 1,Cone-rod dystrophy 6,Leber congenital amaurosis 1,Night blindness, congenital stationary, type 1I] | | | 0 |
| chr17 | 48504265 | *ACSF2* | NM_001288968.1:c.129-1G>C | | splice_acceptor_variant&intron_variant | rs189245546 | 610465 | 0.048 | 0.032011 | 0.0086 |
| chr17 | 48629001 | *SPATA20* | NM_022827.3:c.1706G>A | NM_022827.3:p.Arg569Gln | Missense | rs144320831 | 613939; n/a | 5.669 | 7.69479 | 0.001 |
| chr19 | 52497739 | *ZNF615* | NM_001321323.1:c.638C>T | NM_001321323.1:p.Thr213Ile | Missense | rs369585230 | | -2.753 | -1.16086 | 0.0001 |
| chr19 | 54561565 | *VSTM1* | NM_198481.3:c.349delG | NM_198481.3:p.Val117fs | Frameshift | rs745734767 | 616804 | | | 0.0001 |
| chr2 | 197537074 | *CCDC150* | NM_001080539.1:c.942_943delGCinsTT | NM_001080539.1:p.LeuGln314* | Stop gain | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|
| chr2 | 210881322 | *RPE* | NM_001318926.1:c.488C>T | NM_001318926.1:p.Pro163Leu | Missense | rs370757730 | 180480; 613833 | 4.96 | 7.33988 | 0.0001 |
| chr4 | 83424050 | *TMEM150C* | NM_001080506.1:c.165A>C | NM_001080506.1:p.Ile55Ile | Splice region variant & synonymous variant | rs377209343 | 617292 | | | 0.0004 |
| chr6 | 32489844 | *HLA-DRB5* | NM_002125.3:c.206_208delTCGinsACA | NM_002125.3:p.PheAsp69TyrAsn | Missense | | 604776 | | | |
| chr6 | 100838957 | *SIM1* | NM_005068.2:c.1581T>A | NM_005068.2:p.His527Gln | Missense | | 603128 | 0.644 | 3.55834 | |
| **chr7** | **16837300** | ***AGR2*** | **NM_006408.4:c.349C>T** | **NM_006408.4:p.His117Tyr** | **Missense** | **rs780638101** | **606358** | **3.236** | **6.07564** | **0.0001** |
| chr7 | 20824043 | *SP8* | NM_182700.5:c.1387_1392delGGCGGC | NM_182700.5:p.Gly463_Gly464del | Conservative inframe deletion | rs759086117 | 608306 | | | 0.0057 |
| chrX | 39932647 | *BCOR* | NM_001123385.1:c.1952T>C | NM_001123385.1:p.Ile651Thr | Missense | rs746064364 | 300485 [Microphthalmia, syndromic 2] | 8.942 | 3.8841 | 0 |
| **Family 3 - 2399903** | | | | | | | | | | |
| chr1 | 3417196 | *MEGF6* | NM_001409.3:c.2707+1G>A | | Splice donor & intron | rs546771819 | 604266 | 5.977 | 4.01321 | 0 |
| chr1 | 3732033 | *CEP104* | NM_014704.3:c.2711G>T | NM_014704.3:p.Gly904Val | Missense | | 616690 [Joubert syndrome 25] | 4.719 | 5.62154 | |
| chr14 | 94517551 | *DDX24* | NM_020414.3:c.2566A>G | NM_020414.3:p.Thr856Ala | Missense | | 606181; 608338 | -0.329 | 1.18224 | |
| chr3 | 165491198 | *BCHE* | NM_000055.3:c.1781G>T | NM_000055.3:p.Ser594Ile | Missense | rs142859898 | 177400 [Apnea, postanesthetic, susceptibility to, due to BCHE deficiency,Butyrylcholinesterase deficiency] | 3.448 | 5.89742 | 0.0009 |
| **chr7** | **16837300** | ***AGR2*** | **NM_006408.4:c.349C>T** | **NM_006408.4:p.His117Tyr** | **Missense** | **rs780638101** | **606358** | **3.236** | **6.07564** | **0.0001** |
| chrX | 36053879 | *CFAP47* | NM_001304548.1:c.3719A>G | NM_001304548.1:p.Lys1240Arg | Missense | | | 0.686 | | |
| **Family 4 - 2337168** | | | | | | | | | | |
| chr1 | 79116314 | *IFI44* | NM_006417.4:c.434A>T | NM_006417.4:p.Asp145Val | Missense | rs146103588 | 610468; 613975 | 3.127 | 4.4882 | 0.0019 |
| chr14 | 88945502 | *PTPN21* | NM_007039.3:c.2273T>C | NM_007039.3:p.Leu758Pro | Missense | | 603271 | 1.421 | 0.730167 | |
| chr16 | 461495 | *DECR2* | NM_020664.3:c.796G>C | NM_020664.3:p.Val266Leu | Missense | | 615839 | 6.656 | 3.47079 | |
| chr16 | 720513 | *RHOT2* | NM_138769.2:c.496G>A | NM_138769.2:p.Val166Ile | Missense | rs146373820 | 613889; 618290 | 9.856 | 4.17403 | 0 |
| chr16 | 1498755 | *CLCN7* | NM_001287.5:c.1810A>G | NM_001287.5:p.Met604Val | Missense | | 602727 [Hypopigmentation, organomegaly, and delayed myelination and development,Osteopetrosis, autosomal dominant 2,Osteopetrosis, autosomal recessive 4]; 618740 | 2.031 | 1.60287 | |
| chr16 | 16355487 | *NOMO3* | NM_001004067.3:c.1349A>G | NM_001004067.3:p.His450Arg | Missense | rs750513109 | 609159 | 3.811 | -0.22054 | 0 |
| chr17 | 6928019 | *BCL6B* | ENST00000293805.5:c.720_731delCAGCAGCAGCAG | ENST00000293805.5:p.Ser241_Ser244del | Disruptive inframe deletion | | 608992 | | | |

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|---|---|---|---|---|---|---|---|---|---|---|
| chr17 | 7918378 | *GUCY2D* | NM_000180.3:c.2769+9T>G | | Splice region & intron | rs771741738 | 600179 [?Choroidal dystrophy, central areolar 1,Cone-rod dystrophy 6,Leber congenital amaurosis 1,Night blindness, congenital stationary, type 1I] | | | 0 |
| chr17 | 56429356 | *TSPOAP1-AS1* | NR_038410.1:n.755-4A>G | | Splice region & intron | | n/a; 603555; 612482 [Sessile serrated polyposis cancer syndrome] | | | |
| chr17 | 76502807 | *DNAH17* | NM_173628.3:c.4798G>T | NM_173628.3:p.Val1600Leu | Missense | rs76449350 | 610063 [Spermatogenic failure 39]; n/a | 0.71 | 3.12798 | 0.0091 |
| chr18 | 10800427 | *PIEZO2* | NM_022068.2:c.1286T>C | NM_022068.2:p.Ile429Thr | Missense | | 613629 [?Marden-Walker syndrome,Arthrogryposis, distal, type 3,Arthrogryposis, distal, type 5,Arthrogryposis, distal, with impaired proprioception and touch] | 6.467 | 2.96644 | |
| chr19 | 6047495 | *RFX2* | NM_000635.3:c.13G>A | NM_000635.3:p.Glu5Lys | Missense | rs142338131 | 142765 | 7.211 | 7.44236 | 0.0045 |
| chr19 | 8400050 | *KANK3* | NM_198471.2:c.661A>G | NM_198471.2:p.Lys221Glu | Missense | | 614611 | 4.529 | 4.76978 | |
| chr19 | 8577979 | *ZNF414* | NM_001146175.1:c.250G>A | NM_001146175.1:p.Gly84Ser | Missense | rs772627384 | | -0.205 | 1.02072 | 0 |
| chr19 | 9061720 | *MUC16* | NM_024690.2:c.25726T>C | NM_024690.2:p.Phe8576Leu | Missense | rs776428876 | 606154 | -0.753 | 0.126963 | 0.0001 |
| chr19 | 9204530 | *OR1M1* | NM_001004456.1:c.610G>A | NM_001004456.1:p.Gly204Arg | Missense | rs199800381 | | -3.28 | 3.31593 | 0.0011 |
| chr19 | 14236925 | *ASF1B* | NM_018154.2:c.225+9G>A | | Splice region & intron | rs543610465 | 609190 | | | |
| chr19 | 18391795 | *JUND* | NM_005354.5:c.491_499dupCCGCCGCCG | NM_005354.5:p.Ala164_Ala166dup | Conservative inframe insertion | rs529130306 | 165162; n/a | | | 0.021 |
| chr20 | 5935314 | *MCM8* | NM_001281521.1:c.314G>A | NM_001281521.1:p.Arg105Lys | Missense | | 608187 [?Premature ovarian failure 10]; n/a | 0.392 | 0.145186 | |
| chr20 | 9440301 | *PLCB4* | NM_000933.3:c.3056A>G | NM_000933.3:p.Gln1019Arg | Missense | rs377707845 | 600810 [Auriculocondylar syndrome 2] | 6.823 | 2.71346 | 0.0024 |
| chr20 | 39990473 | *EMILIN3* | NM_052846.1:c.1736C>T | NM_052846.1:p.Ser579Leu | Missense | rs772266071 | 608929; 605520 | 7.181 | 5.3479 | 0 |
| chr3 | 130134482 | *COL6A5* | NM_001278298.1:c.4762-7A>G | | Splice region & intron | rs575983094 | 611916 | | | 0.0072 |
| chr5 | 66478938 | *CD180* | NM_005582.2:c.1733C>T | NM_005582.2:p.Pro578Leu | Missense | rs185244476 | 602226 | 5.621 | 5.62279 | 0.0011 |
| chr5 | 72875903 | *UTP15* | NM_032175.3:c.1541A>C | NM_032175.3:p.Lys514Thr | Missense | rs142841898 | 616194 | 0.367 | 1.87684 | 0.0008 |
| chr7 | 20824043 | *SP8* | NM_182700.5:c.1387_1392delGGCGGC | NM_182700.5:p.Gly463_Gly464del | Conservative inframe deletion | rs759086117 | 608306 | | | 0.0057 |
| chr7 | 103835705 | *ORC5* | NM_002553.3:c.442-3C>T | | Splice region & intron | rs747497110 | 602331 | | | 0.0003 |
| chr7 | 107334923 | *SLC26A4* | NM_000441.1:c.1339_1340delAAinsTCT | NM_000441.1:p.Lys447fs | Frameshift & missense & splice region | | 605646 [Deafness, autosomal recessive 4, with enlarged vestibular aqueduct, Pendred syndrome] | | | |
| chr7 | 107334924 | *SLC26A4* | NM_000441.1:c.1340_1341insTCT | NM_000441.1:p.Lys447delinsAsnLeu | Splice region & disruptive inframe insertion | | 605646 [Deafness, autosomal recessive 4, with enlarged vestibular aqueduct,Pendred syndrome] | | | |

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|---|---|---|---|---|---|---|---|---|---|---|
| chr7 | 116199040 | *CAV1* | NM_001753.4:c.236A>G | NM_001753.4:p.His79Arg | Missense | rs376004565 | 601047 [?Lipodystrophy, congenital generalized, type 3,Lipodystrophy, familial partial, type 7,Pulmonary hypertension, primary, 3] | 8.947 | 3.18652 | 0.0005 |
| chr7 | 121678816 | *PTPRZ1* | NM_002851.2:c.5375A>G | NM_002851.2:p.Asn1792Ser | Missense | | 176891 | 6.197 | 3.58104 | |
| **chr7** | **16837300** | ***AGR2*** | **NM_006408.4:c.349C>T** | **NM_006408.4:p.His117Tyr** | **Missense** | **rs780638101** | **606358** | **3.236** | **6.07564** | **0.0001** |
| chr8 | 21955123 | *FAM160B2* | NM_022749.5:c.394C>T | NM_022749.5:p.Pro132Ser | Missense | rs371809549 | | 6.142 | 5.48401 | 0.0003 |
| chr9 | 139298499 | *ENTR1* | NM_001039707.1:c.1208+8C>T | | Splice region & intron | | 618289 | | | |
| chr9 | 140267963 | *EXD3* | NM_017820.4:c.209G>A | NM_017820.4:p.Arg70Gln | Missense | rs200718958 | | -0.133 | 1.33609 | 0.0036 |
| **Family 5 - 2151518** | | | | | | | | | | |
| chr7 | 24745875 | *GSDME* | NM_001127453.1:c.1111T>G | NM_001127453.1:p.Cys371Gly | Missense | rs138301435 | 608798 [Deafness, autosomal dominant 5] | -2.439 | -3.47024 | 0.0023 |
| **chr7** | **16839367** | ***AGR2*** | **NM_006408.4:c.330+1G>T** | | **Splice donor & intron** | **rs1483660993** | **606358** | **6.2** | **5.1938** | |
| **Family 7 - 2518771 – index and sister** | | | | | | | | | | |
| chr10 | 31137766 | *ZNF438* | NM_001143766.1:c.1568G>A | NM_001143766.1:p.Arg523Gln | Missense | rs745473764 | | 0.854 | 1.66277 | 0.0001 |
| chr10 | 32580137 | *EPC1* | NM_025209.3:c.929T>G | NM_025209.3:p.Phe310Cys | Missense | rs868826577 | 610999 | 3.411 | 4.08598 | |
| chr10 | 37482114 | *ANKRD30A* | NM_052997.2:c.2374G>T | NM_052997.2:p.Ala792Ser | Missense | rs189204441 | 610856 | -0.491 | -1.68588 | 0.015 |
| chr10 | 45473142 | *DEPP1* | NM_007021.3:c.337C>T | NM_007021.3:p.Gln113* | stop_gained | rs867293581 | 611309 | 3.966 | 11.5352 | |
| chr10 | 45959681 | *MARCHF8* | NM_001282866.1:c.242+6A>G | | splice_region_variant&intron_variant | rs115355800 | 613335 | | | 0.022 |
| chr10 | 50819325 | *SLC18A3* | NM_003055.2:c.539C>G | NM_003055.2:p.Ala180Gly | Missense | rs771402838 | 600336 [Myasthenic syndrome, congenital, 21, presynaptic]; 118490 [Myasthenic syndrome, congenital, 6, presynaptic] | 3.537 | 3.50895 | 0.0002 |
| chr10 | 50943403 | *OGDHL* | NM_018245.2:c.2910-6C>T | | splice_region_variant&intron_variant | | 617513 | | | |
| chr10 | 52569761 | *A1CF* | NM_001198819.1:c.1550A>C | NM_001198819.1:p.Glu517Ala | Missense | | 618199 | 7.674 | 6.41814 | |
| chr10 | 52610477 | *A1CF* | NM_001198819.1:c.71A>G | NM_001198819.1:p.Lys24Arg | Missense | | 618199 | -1.819 | -1.58506 | |
| chr12 | 14599904 | *ATF7IP* | NM_181352.1:c.1954-8_1954-4dupTTTTT | | splice_region_variant&intron_variant | | 613644 | | | |
| chr14 | 35739656 | *PRORP* | NM_014672.3:c.1474C>A | NM_014672.3:p.His492Asn | Missense | | 609947 | 3.207 | 6.351 | |
| chr14 | 105417623 | *AHNAK2* | NM_138420.2:c.4165G>C | NM_138420.2:p.Ala1389Pro | Missense | | 608570 | -0.362 | 2.02195 | |
| chr17 | 27620989 | *NUFIP2* | NM_020772.2:c.86_88dupAGC | NM_020772.2:p.Gln29dup | conservative_inframe_insertion | rs577779578 | 609356 | | | 0.003 |
| chr17 | 28791746 | *CPD* | NM_001304.4:c.4057A>G | NM_001304.4:p.Thr1353Ala | Missense | rs115003383 | 603102 | 8.469 | 4.03671 | 0.011 |

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|---|---|---|---|---|---|---|---|---|---|---|
| chr17 | 29685568 | *NF1* | NM_001042492.2:c.8041A>G | NM_001042492.2:p.Ile2681Val | Missense | rs146315101 | 613113 [Leukemia, juvenile myelomonocytic,Neurofibromatosis-Noonan syndrome,Neurofibromatosis, familial spinal,Neurofibromatosis, type 1,Watson syndrome] | 3.221 | -0.019102 | 0.0011 |
| chr17 | 33904517 | *PEX12* | NM_000286.2:c.220T>C | NM_000286.2:p.Tyr74His | Missense | | 601758 [Peroxisome biogenesis disorder 3A (Zellweger),Peroxisome biogenesis disorder 3B] | 8.495 | 5.48378 | |
| chr17 | 36485313 | *GPR179* | NM_001004334.3:c.4139C>T | NM_001004334.3:p.Pro1380Leu | Missense | rs764207680 | 614515 [Night blindness, congenital stationary (complete), 1E, autosomal recessive] | 0.455 | 0.154142 | 0.0001 |
| chr18 | 14852348 | *ANKRD30B* | NM_001145029.1:c.4048G>A | NM_001145029.1:p.Glu1350Lys | Missense | | 616565 | 4.374 | 3.9738 | |
| chr18 | 21660713 | *TTC39C* | NM_001135993.1:c.625G>A | NM_001135993.1:p.Glu209Lys | Missense | | | 3.464 | 2.01257 | |
| chr4 | 128625370 | *INTU* | NM_015693.3:c.1504-8delT | | splice_region_variant&intron_variant | rs772920778 | 610621 [?Orofaciodigital syndrome XVII,?Short-rib thoracic dysplasia 20 with polydactyly] | | | 0.0059 |
| chr7 | 132070014 | *PLXNA4* | NM_001105543.1:c.1412C>T | NM_001105543.1:p.Thr471Met | Missense | rs183271681 | 604280 | -0.687 | -0.047923 | 0.0074 |
| **chr7** | **16837300** | ***AGR2*** | **NM_006408.3:c.349C>T** | **NM_006408.3:p.His117Tyr** | **Missense** | **rs780638101** | **606358** | **3.236** | **6.07564** | **0.0001** |
| chr9 | 19346501 | *DENND4C* | NM_017925.6:c.3587A>G | NM_017925.6:p.Asp1196Gly | Missense | rs149094194 | | 5.795 | 2.19924 | 0.0011 |
| chrX | 65252335 | *VSIG4* | NM_007268.2:c.669C>A | NM_007268.2:p.Ser223Arg | Missense | rs749453785 | 300353 | -1.006 | 2.20312 | 0 |
| chrX | 153880610 | *CTAG2* | NM_020994.4:c.565G>T | NM_020994.4:p.Glu189* | stop_gained | | 300396 | -1.488 | 6.97086 | |
| **Family 8 - 2508357** | | | | | | | | | | |
| chr1 | 69369 | *OR4F5* | NM_001005484.1:c.279G>T | NM_001005484.1:p.Gln93His | Missense | | | 0.502 | 3.75252 | |
| chr1 | 180464666 | *ACBD6* | NM_032360.3:c.223-6A>G | | Splice region & intron | rs151129855 | 616352 | | | 0.0038 |
| chr1 | 197871814 | *C1orf53* | NM_001024594.2:c.35C>T | NM_001024594.2:p.Ala12Val | Missense | rs374493997 | | 0.447 | 0.697828 | 0.0092 |
| chr1 | 197887095 | *LHX9* | NM_020204.2:c.142G>A | NM_020204.2:p.Ala48Thr | Missense | rs113693840 | 606066 | 6.277 | 2.96391 | 0.011 |
| chr1 | 200584666 | *KIF14* | NM_014875.2:c.1184C>T | NM_014875.2:p.Thr395Met | Missense | rs138621008 | 611279 [?Meckel syndrome 12,Microcephaly 20, primary, autosomal recessive] | 3.493 | 2.47981 | 0.011 |
| chr1 | 201190604 | *IGFN1* | NM_001164586.1:c.9931A>G | NM_001164586.1:p.Thr3311Ala | Missense | rs370519814 | 617309 | 4.578 | 3.80368 | 0.0008 |
| chr1 | 203743568 | *LAX1* | NM_017773.3:c.956G>C | NM_017773.3:p.Gly319Ala | Missense | rs755267095 | | 0.304 | -0.857094 | 0.0002 |
| chr1 | 207642169 | *CR2* | NM_001006658.2:c.659G>A | NM_001006658.2:p.Arg220Gln | Missense | rs147633291 | 120650 [Systemic lupus erythematosus, susceptibility to, 9,Immunodeficiency, common variable, 7] | -0.236 | -0.85175 | 0.0002 |

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|---|---|---|---|---|---|---|---|---|---|---|
| chr1 | 207651374 | *CR2* | NM_001006658.2:c.3047C>T | NM_001006658.2:p.Ser1016Leu | Missense | rs138062179 | 120650 [Systemic lupus erythematosus, susceptibility to, 9,Immunodeficiency, common variable, 7] | 0.006 | 1.26183 | 0.0038 |
| chr1 | 214638055 | *PTPN14* | NM_005401.4:c.92A>G | NM_005401.4:p.Asn31Ser | Missense | rs151121546 | 603155 [Choanal atresia and lymphedema] | 2.19 | 0.070051 | 0.0008 |
| chr1 | 219352740 | *LYPLAL1* | NM_001350628.1:c.192-2A>G | | Splice acceptor & intron | rs530475818 | 616548 | | | 0.0008 |
| chr1 | 220300171 | *IARS2* | NM_018060.3:c.1823C>G | NM_018060.3:p.Ser608Cys | Missense | | 612801 [?Cataracts, growth hormone deficiency, sensory neuropathy, sensorineural hearing loss, and skeletal dysplasia] | 2.424 | 5.65751 | |
| chr1 | 220324939 | *RAB3GAP2* | NM_012414.3:c.4026+9A>G | | Splice region & intron | | 609275 [Martsolf syndrome,Warburg micro syndrome 2] | | 0.18342 | |
| chr1 | 228494751 | *OBSCN* | NM_001271223.2:c.14947A>G | NM_001271223.2:p.Met4983Val | Missense | | 608616 | 3.952 | 3.31168 | |
| chr1 | 228560723 | *OBSCN* | NM_001271223.2:c.25115G>A | NM_001271223.2:p.Arg8372His | Missense | rs772771183 | 608616 | 0.06 | 6.83572 | 0.0001 |
| chr10 | 115391287 | *NRAP* | NM_001261463.1:c.1823T>C | NM_001261463.1:p.Ile608Thr | Missense | rs867292545 | 602873 | 6.616 | 5.40354 | |
| chr10 | 118618610 | *ENO4* | NM_001242699.1:c.595C>T | NM_001242699.1:p.Pro199Ser | Missense | rs150721071 | 131375 | 1.127 | 2.55975 | 0.0061 |
| chr11 | 556970 | *LRRC56* | NM_173573.2:c.841G>A | NM_173573.2:p.Ala281Thr | Missense | rs200530408 | 618227 [Ciliary dyskinesia, primary, 39] | -3.775 | 0.407053 | 0.0015 |
| chr11 | 615268 | *IRF7* | NM_001572.3:c.21-9C>T | | Splice region & intron | rs775307916 | 605047 [?Immunodeficiency 39] | | 4.43317 | 0 |
| chr11 | 637408 | *DRD4* | NM_000797.3:c.104C>T | NM_000797.3:p.Ala35Val | Missense | rs767779176 | 126452 [Attention deficit-hyperactivity disorder,Autonomic nervous system dysfunction] | -0.436 | | 0.0009 |
| chr11 | 640063 | *DRD4* | NM_000797.3:c.814G>C | NM_000797.3:p.Gly272Arg | Missense | | 126452 [Attention deficit-hyperactivity disorder,Autonomic nervous system dysfunction] | -0.327 | -1.0774 | |
| chr11 | 640167 | *DRD4* | NM_000797.3:c.918_925delCGGCTCCAinsTGGCCCCG | NM_000797.3:p.CysGlySerAsn306CysGlyProAsp | Missense | | 126452 [Attention deficit-hyperactivity disorder,Autonomic nervous system dysfunction] | | 3.0393 | |
| chr11 | 704536 | *EPS8L2* | NM_001276274.1:c.742G>A | NM_001276274.1:p.Ala248Thr | Missense | rs140750324 | 614988 [Deafness autosomal recessive 106] | | | 0.0053 |
| chr11 | 798222 | *SLC25A22* | NM_001293167.1:c.610_612dupCGC | NM_001293167.1:p.Arg204dup | Conservativeinframe inser tion | rs572464433 | 609302 [Epileptic encephalopathy, early infantile, 3] | | 1.3418 | 0.003 |
| chr11 | 1028702 | *MUC6* | NM_005961.2:c.1535G>A | NM_005961.2:p.Arg512His | Missense | rs748763819 | 158374 | -1.055 | 2.60293 | 0.0001 |
| chr11 | 1093705 | *MUC2* | ENST00000441003.2:c.5524G>T | ENST00000441003.2:p.Ala1842Ser | Missense | rs546395242 | 158370 | | | 0.0008 |
| chr11 | 1103869 | *MUC2* | ENST00000441003.2:c.8168C>T | ENST00000441003.2:p.Ser2723Leu | Missense | rs770253933 | 158370 | | -0.95932 | 0.0013 |
| chr11 | 1156634 | *MUC5AC* | XM_003403450.4:c.1482G>A | XM_003403450.4:p.Met494Ile | Missense | rs747862882 | 158373 | -0.554 | | 0 |
| chr11 | 1157570 | *MUC5AC* | XM_003403450.4:c.1582C>A | XM_003403450.4:p.Pro528Thr | Missense | rs145633450 | 158373 | 2.484 | | 0.0008 |

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|---|---|---|---|---|---|---|---|---|---|---|
| chr11 | 13729560 | *FAR1* | NM_032228.5:c.479G>A | NM_032228.5:p.Arg160His | Missense | rs139416149 | 616107 [Peroxisomal fatty acyl-CoA reductase 1 disorder] | 5.818 | 1.02607 | 0.001 |
| chr11 | 28135086 | *METTL15* | NM_001113528.1:c.205G>A | NM_001113528.1:p.Ala69Thr | Missense | rs150513835 | 618711 | -0.107 | 0.403354 | 0.012 |
| chr11 | 44331153 | *ALX4* | NM_021926.3:c.460T>A | NM_021926.3:p.Cys154Ser | Missense | rs182274454 | 605420 [Craniosynostosis 5, susceptibility to,Frontonasal dysplasia 2,Parietal foramina 2] | 6.759 | | 0.0079 |
| chr11 | 57077855 | *TNKS1BP1* | NM_033396.2:c.2330A>C | NM_033396.2:p.Lys777Thr | Missense | rs150510361 | 607104 | -0.909 | -1.54772 | 0.0045 |
| chr11 | 64132915 | *RPS6KA4* | NM_003942.2:c.1049C>T | NM_003942.2:p.Pro350Leu | Missense | rs141809902 | 603606 | 4.182 | 0.186073 | 0.0064 |
| chr11 | 70277319 | *CTTN* | NM_001184740.1:c.1088A>G | NM_001184740.1:p.Gln363Arg | Missense | rs141534651 | 164765 | 1.569 | | 0.0024 |
| chr11 | 117052513 | *SIDT2* | NM_001040455.1:c.306-10C>T | | Splice region & intron | rs183950705 | 617551 | | -1.20542 | 0.011 |
| chr12 | 2027813 | *CACNA2D4* | NM_172364.4:c.-174C>T | | 5 prime UTR premature start codon gain | rs374494829 | 608171 [Retinal cone dystrophy 4] | | 5.84564 | 0.0083 |
| chr12 | 2775846 | *CACNA1C* | NM_199460.2:c.4671-6T>A | | Splice region & intron | | 114205 [Brugada syndrome 3,Long QT syndrome 8,Timothy syndrome] | | 6.05791 | |
| chr12 | 2997396 | *RHNO1* | NM_001252499.2:c.488C>T | NM_001252499.2:p.Ser163Leu | Missense | rs145733432 | 614085 | 1.743 | 2.7842 | 0.0015 |
| chr12 | 120794697 | *MSI1* | NM_002442.3:c.652+8C>T | | Splice region & intron | rs145402971 | 603328 | | -0.392542 | 0.0084 |
| chr12 | 124297973 | *DNAH10* | NM_207437.3:c.3053G>A | NM_207437.3:p.Cys1018Tyr | Missense | rs138151312 | 605884 | 6.743 | 2.54644 | 0.0048 |
| chr12 | 124364296 | *DNAH10* | NM_207437.3:c.8228C>T | NM_207437.3:p.Pro2743Leu | Missense | rs755673190 | 605884 | 2.659 | 2.82796 | 0.0001 |
| chr14 | 89044465 | *ZC3H14* | NM_024824.4:c.1260T>G | NM_024824.4:p.Asp420Glu | Missense | rs201108116 | 613279 [Mental retardation, autosomal recessive 56] | 0.159 | 3.26121 | 0.0003 |
| chr16 | 11370095 | *PRM2* | NM_001286356.1:c.133G>A | NM_001286356.1:p.Glu45Lys | Missense | rs768731173 | 182890 | 0.205 | -0.25231 | 0.0001 |
| chr17 | 28511782 | *NSRP1* | NM_032141.3:c.767C>T | NM_032141.3:p.Ala256Val | Missense | rs148657875 | 616173 | 4.478 | -0.748862 | 0.0014 |
| chr17 | 48632896 | *SPATA20* | NM_022827.3:c.2282G>C | NM_022827.3:p.Arg761Pro | Missense | rs373370910 | 613939 | 3.363 | | 0 |
| chr19 | 362273 | *THEG* | NM_016585.4:c.1067C>G | NM_016585.4:p.Pro356Arg | Missense | rs780542408 | 609503 | 0.29 | 6.78287 | 0 |
| chr19 | 507696 | *MADCAM1* | NM_033513.2:c.190A>G | NM_033513.2:p.Ile64Val | Missense | rs760844827 | 102670 | 2.559 | 4.54354 | 0.0006 |
| chr19 | 871258 | *MED16* | NM_005481.2:c.2099-7_2099-6delTC | | Splice region & intron | | 604062 | | | |
| chr19 | 1061796 | *ABCA7* | NM_019112.3:c.5479G>C | NM_019112.3:p.Gly1827Arg | Missense | | 605414 [Alzheimer disease 9, susceptibility to] | 9.312 | 7.29201 | |
| chr19 | 1487830 | *REEP6* | NM_017573.4:c.547T>G | NM_017573.4:p.Tyr183Asp | Missense | rs202179680 | 609346 [Retinitis pigmentosa 77] | -0.13 | 0.852528 | 0.0033 |
| chr19 | 1556218 | *MEX3D* | NM_001174118.1:c.1300T>C | NM_001174118.1:p.Phe434Leu | Missense | rs746484985 | 611009 | 3.222 | 4.57011 | 0 |
| chr19 | 2763724 | *SGTA* | NM_003021.3:c.424G>A | NM_003021.3:p.Ala142Thr | Missense | rs374479958 | 603419 | 0.338 | 4.70748 | 0.0008 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| chr19 | 2934729 | *ZNF77* | NM_021217.2:c.396C>A | NM_021217.2:p.His132Gln | Missense | rs34184381 | 194551 | -2.339 | 2.49175 | 0.011 |
| chr19 | 55870332 | *COX6B2* | NM_001145402.1:c.1904C>T | NM_001145402.1:p.Ala635Val | Missense | rs148112323 | 618127 | -1.76 | -1.57011 | 0.014 |
| chr19 | 55870797 | *COX6B2* | NM_001145402.1:c.1439G>A | NM_001145402.1:p.Arg480Gln | Missense | rs140308319 | 618127 | -1.188 | | 0.03 |
| chr2 | 85778964 | *GGCX* | NM_000821.6:c.1580C>T | NM_000821.6:p.Thr527Ile | Missense | rs78504541 | 137167 [Pseudoxanthoma elasticum-like disorder with multiple coagulation factor deficiency,Vitamin K-dependent clotting factors, combined deficiency of, 1] | 7.311 | | 0.0095 |
| chr2 | 87072063 | *CD8B* | NM_172213.3:c.602G>A | NM_172213.3:p.Arg201Gln | Missense | | 186730 | 1.112 | | |
| chr2 | 99012373 | *CNGA3* | NM_001298.2:c.740C>T | NM_001298.2:p.Thr247Met | Missense | rs148616345 | 600053 [Achromatopsia 2] | 0.357 | 2.63198 | 0.005 |
| chr2 | 105956062 | *C2orf49* | NM_024093.2:c.122A>T | NM_024093.2:p.Asp41Val | Missense | rs147396516 | | 3.837 | | 0.0009 |
| chr2 | 109365537 | *RANBP2* | NM_006267.4:c.1225A>G | NM_006267.4:p.Ile409Val | Missense | rs201087513 | 601181 [Encephalopathy, acute, infection-induced, 3, susceptibility to] | -0.064 | | 0.0011 |
| chr2 | 116572446 | *DPP10* | NM_001321905.1:c.1829A>G | NM_001321905.1:p.Asn610Ser | Missense | rs373895432 | 608209 | 2.901 | -0.908639 | 0.0002 |
| chr2 | 118587033 | *DDX18* | NM_006773.3:c.1861G>C | NM_006773.3:p.Val621Leu | Missense | | 606355 | 9.184 | 4.64068 | |
| chr2 | 132021201 | *POTEE* | NM_001083538.1:c.2173G>A | NM_001083538.1:p.Asp725Asn | Missense | | 608914 | 5.197 | 0.55247 | |
| chr2 | 238977928 | *SCLY* | NR_037904.1:n.880-10A>G | | Splice region & Intron | | 611056 | | 0.255702 | |
| chr21 | 46913070 | *COL18A1* | ENST00000359759.8:c.3460-7A>T | | Splice region & intron | rs576172127 | 120328 [Glaucoma, primary closed-angle,Knobloch syndrome, type 1] | | 2.29856 | 0.001 |
| chr3 | 9959601 | *IL17RC* | NM_153461.3:c.341-6A>G | | Splice region & Intron | | 610925 [Candidiasis, familial, 9] | | | |
| chr3 | 10420100 | *ATP2B2* | NM_001001331.2:c.1043-6C>G | | Splice region & intron | rs111358898 | 108733 [Deafness, autosomal recessive 12, modifier of] | | 4.79197 | 0.011 |
| chr3 | 12641745 | *RAF1* | NM_002880.3:c.896A>G | NM_002880.3:p.Asn299Ser | Missense | rs866428774 | 164760 [Cardiomyopathy, dilated, 1NN, LEOPARD syndrome 2,Noonan syndrome 5] | 2.879 | 0.850035 | |
| chr3 | 15115639 | *RBSN* | NM_001302378.1:c.2005G>A | NM_001302378.1:p.Glu669Lys | Missense | rs368892679 | 609511 | 4.257 | | 0.0001 |
| chr4 | 37446261 | *NWD2* | NM_001144990.1:c.2651C>T | NM_001144990.1:p.Ser884Leu | Missense | rs371806771 | | 5.809 | | 0.0029 |
| chr4 | 38051428 | *TBC1D1* | NM_015173.3:c.1819C>T | NM_015173.3:p.Pro607Ser | Missense | rs766339856 | 609850 | 0.018 | | 0.0002 |
| chr4 | 77138780 | *SCARB2* | NM_001242936.1:c.20G>A | NM_001242936.1:p.Cys7Tyr | Missense | rs576816603 | 602257 [Epilepsy, progressive myoclonic 4, with or without renal failure] | 0.365 | | 0.0008 |
| chr4 | 79308538 | *FRAS1* | NM_025074.6:c.3658G>A | NM_025074.6:p.Val1220Met | Missense | rs367770853 | 607830 [Fraser syndrome 1] | 2.875 | | 0.0001 |
| chr5 | 32263226 | *MTMR12* | NM_001040446.2:c.706T>A | NM_001040446.2:p.Cys236Ser | Missense | rs199989524 | 606501 | 2.52 | | 0.0029 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| chr5 | 45695991 | *HCN1* | NM_021072.3:c.205G>A | NM_021072.3:p.Gly69Ser | Missense | | 602780 [Epileptic encephalopathy, early infantile, 24,Generalized epilepsy with febrile seizures plus, type 10] | 0.064 | | |
| chr5 | 63496630 | *RNF180* | NM_001113561.2:c.1-5C>T | | Splice region & intron | rs145598166 | 616015 | | | 0.0023 |
| chr6 | 137323457 | *IL20RA* | NM_014432.3:c.900C>A | NM_014432.3:p.Phe300Leu | Missense | | 605620 | 1.674 | | |
| chr6 | 147136238 | *ADGB* | NM_024694.3:c.4889C>T | NM_024694.3:p.Ala1630Val | Missense | | 614630 | 2.326 | | |
| chr6 | 149699835 | *TAB2* | NM_001292034.2:c.784T>C | NM_001292034.2:p.Ser262Pro | Missense | | 605101 [Congenital heart defects, nonsyndromic, 2] | 2.941 | | |
| chr6 | 159653708 | *FNDC1* | NM_032532.2:c.2164C>T | NM_032532.2:p.Pro722Ser | Missense | rs767489430 | 609991 | -0.98 | | 0.0005 |
| chr6 | 168439229 | *KIF25* | NM_030615.2:c.318-4G>A | | Splice region & intron | rs376908446 | 603815 | | | 0.001 |
| chr7 | 1522175 | *INTS1* | NM_001080453.2:c.3703+4_3703+7delCGGTinsTGGC | | Splice region & intron | | 611345 [Neurodevelopmental disorder with cataracts, poor growth, and dysmorphic facies] | | | |
| chr7 | 1532637 | *INTS1* | NM_001080453.2:c.2165+9A>G | | Splice region & intron | rs202080075 | 611345 [Neurodevelopmental disorder with cataracts, poor growth, and dysmorphic facies] | | | 0.0008 |
| chr7 | 2695729 | *TTYH3* | NM_025250.2:c.1024C>T | NM_025250.2:p.Pro342Ser | Missense | rs202147266 | 608919 | 2.048 | | |
| chr7 | 4824638 | *AP5Z1* | NM_014855.2:c.890C>G | NM_014855.2:p.Ala297Gly | Missense | | 613653 [Spastic paraplegia 48, autosomal recessive] | 5.732 | | |
| chr7 | 4830809 | *AP5Z1* | NM_014855.2:c.2217C>G | NM_014855.2:p.His739Gln | Missense | | 613653 [Spastic paraplegia 48, autosomal recessive] | 0.228 | | |
| chr7 | 12675734 | *SCIN* | NM_001112706.2:c.1384C>T | NM_001112706.2:p.Arg462Trp | Missense | rs771548886 | 613416 | 1.186 | | 0.0002 |
| **chr7** | **16839366** | ***AGR2*** | **NM_006408.3:c.330+1delG** | | **Splice donor & intron** | | **606358** | | | |
| chr8 | 37706129 | *BRF2* | NM_018310.3:c.199C>T | NM_018310.3:p.Arg67Cys | Missense | rs140395188 | 607013 | 4.524 | | 0.0014 |
| chr8 | 38853939 | *ADAM9* | NM_078473.2:c.20C>T | NM_078473.2:p.Pro7Leu | Missense | rs750181557 | 602713 [Cone-rod dystrophy 9] | 6.11 | | 0.0003 |
| chrX | 48123331 | *SSX1* | NM_001278691.1:c.445_449delGAGAAinsAAGAG | NM_001278691.1:p.GluLys149LysArg | Missense | | 312820 [?Sarcoma, synovial] | | | |
| chrX | 48213442 | *SSX3* | NM_021014.3:c.272G>T | NM_021014.3:p.Gly91Val | Missense | | 300325 | -1.038 | | |
| **Family 9 – 2534592** | | | | | | | | | | |
| chr7 | **16834610** | ***AGR2*** | **NM_006408.3:c.428G>A** | **NM_006408.3:p.Gly143Glu** | **Missense** | **rs923936131** | **606358** | **7.316** | **7.1477** | |
| **chr17** | 55962604 | *CUEDC1* | NM_001271875.1:c.322A>G | NM_001271875.1:p.Ser108Gly | Missense | rs765302468 | | 7.559 | 5.34241 | 0.0001 |

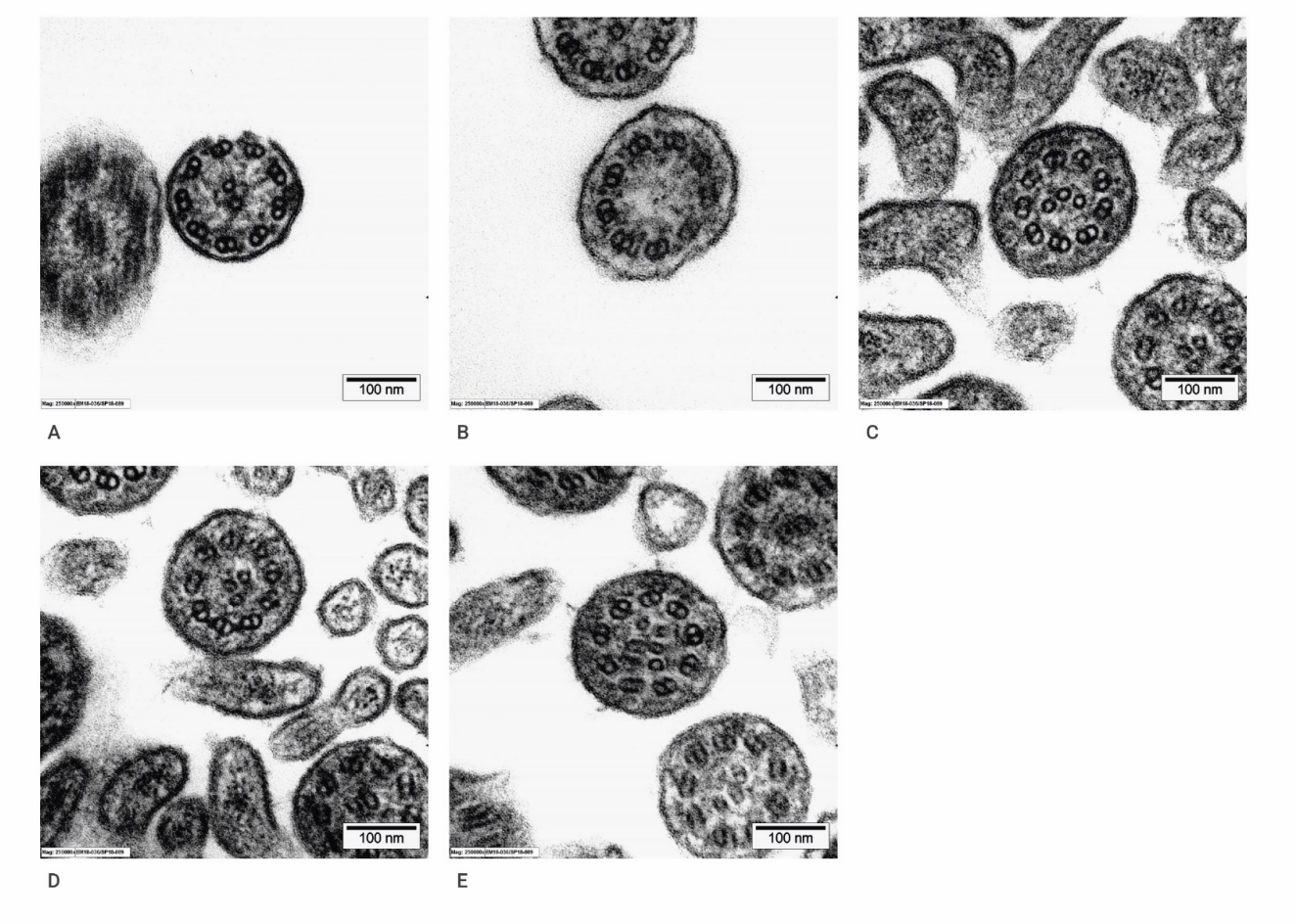
PopMaxFreq (Population maximum frequency - indicates the highest frequency of the variant observed in databases gnomAD, ESP and 1000G). PhyloP scores indicate evolutionary conserved positions (high positive). CADD (Combined Annotation-Dependent Depletion) ranks genetic variants, including single

nucleotide variants (SNVs) and short inserts and deletions (InDels), throughout the human genome reference assembly. [4]RAW score above 4 are considered as likely damaging [4].

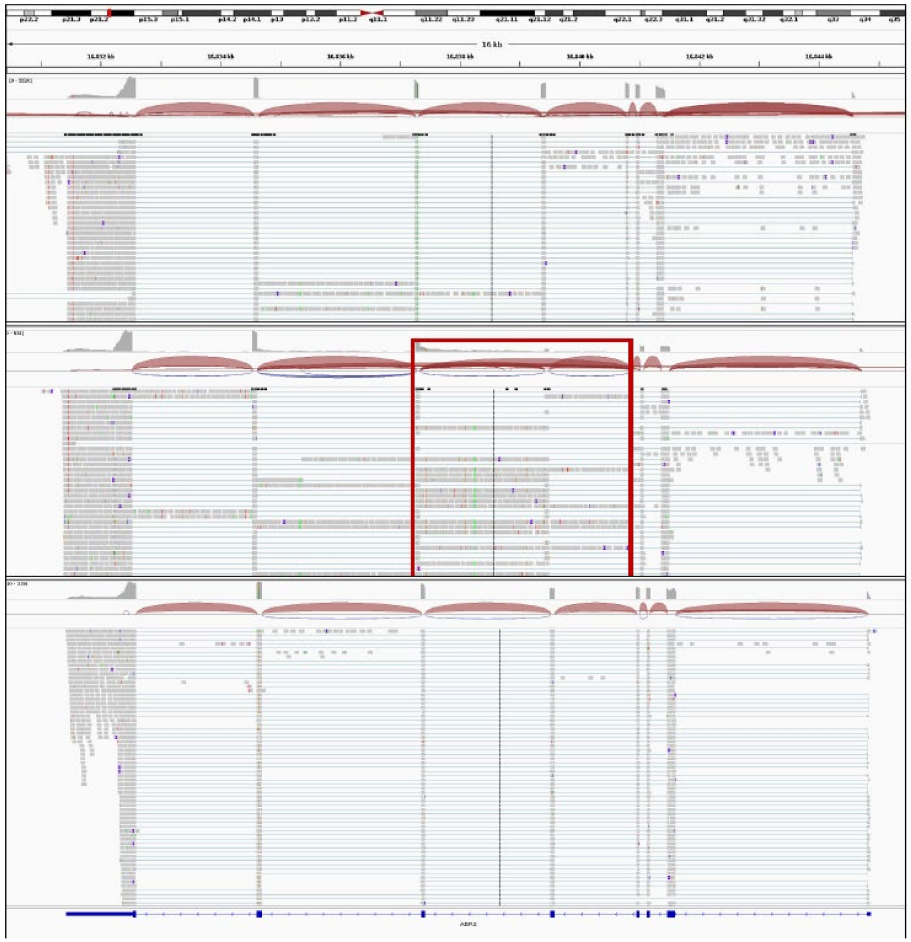
**Supplementary table 3**: AGR2 variants detected in this study are novel or ultra-rare (gnomAD v2.1.1), with high CADD and conservation scores.

| AGR2 Variant (NM_006408.3) | Allele number | Number of homozygotes | Cadd raw | PHRED_CADD | phylop100way_ vertebrate |
|---|---|---|---|---|---|
| c.330+1G>T | 1/249340 | 0 | 5 | 33 | 6 |
| c.330+1del | 0 | 0 | NA | NA | NA |
| c.211C>A, p.Pro71Thr | 0 | 0 | 4 | 27 | 9 |
| c.349C>T, p.His117Tyr | 1/250930 | 0 | 4 | 27 | 3 |
| c.428G>A, p.Gly143Glu | 0 | 0 | 5 | 32 | 7 |

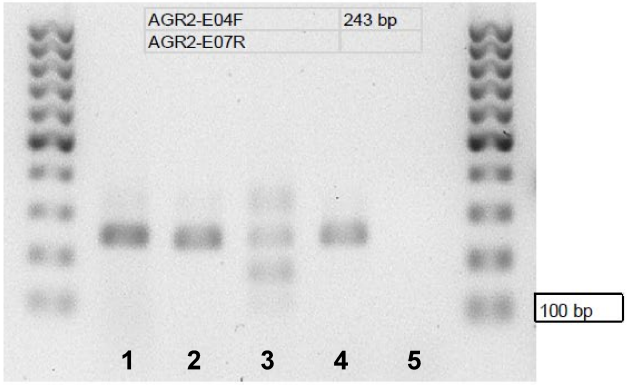
**Supplementary Figure 1.** Electron microscopy findings.in patient II-1 (family 8). A. Control cilia showing nine peripheral and two central pairs of microtubules with outer and inner dynein arms. B. Missing central microtubular doublets. C and D. Triples instead of central doublets with missing dynein arms t peripheral doublets. E. Duplication of central doublets with missing dynein arms at peripheral doublets (250000x).

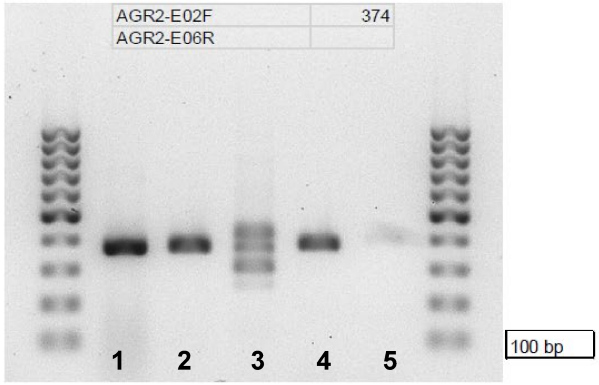


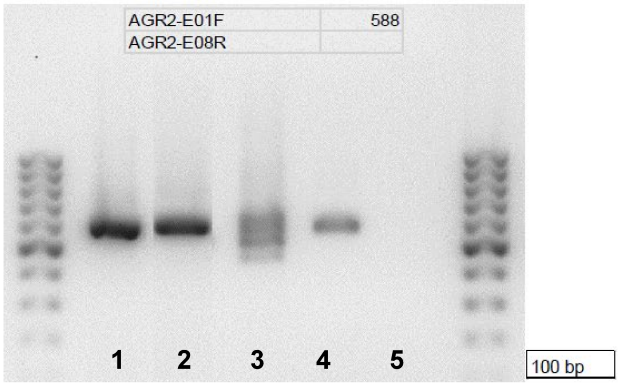
**Supplementary Figure 2A:** Splice junction track from the Integrative Genomic Viewer (IGV), showing *AGR2* RNA sequencing data. Note the aberrant splicing in the sample with the homozygous c.330+1del variant, producing a disturbance in the splicing around intron 5 (red box).



**Supplementary Figure 2B:** The variant c.330+1del lead to abnormal *AGR2* splicing. Agarose gel with bands of expected sizes obtained for samples with the missense variant (exon 4-7, exon2-6, exon 1-8). However, for the patient with the homozygous splicing variant several additional bands are detected, corresponding to abnormal *AGR2* transcripts. No *AGR2* PCR products were detected in blood derived RNA.




Lane 1: Hom. c.349C>T, p.His117Tyr

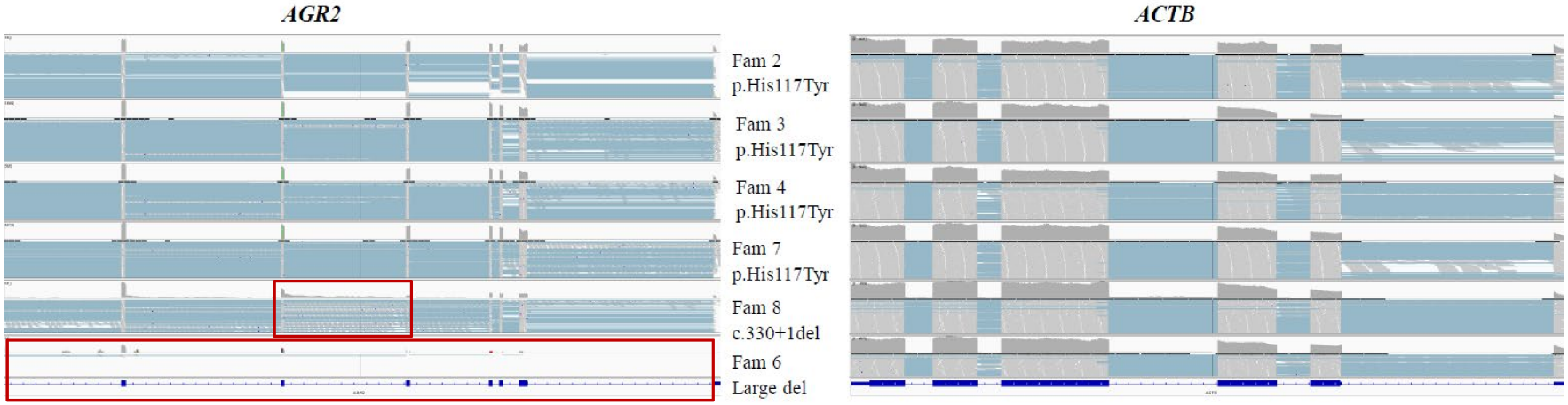
Lane 2: Het. c.349C>T, p.His117Tyr

Lane 3: Hom. c.330+1del

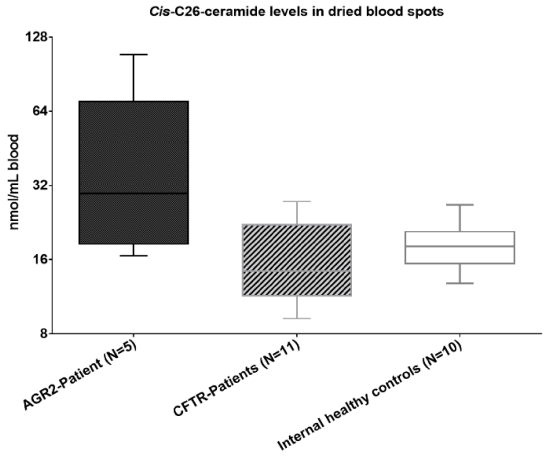
Lane 4: Control

Lane 5: RNA isolated from blood

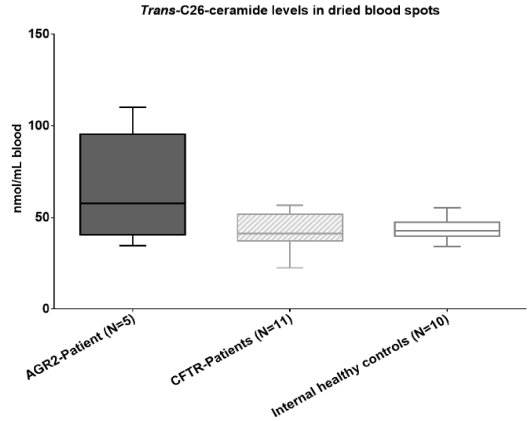
**Supplementary Figure 2C:** IGV tracks showing *AGR2* RNA sequencing data. Left panel is showing the aligned RNAseq data for *AGR2*. Right panel is showing aligned data for the housekeeping gene *ACTB* (as control gene). Note abnormal reads corresponding to intron 5. This is consistent with the retention of the intron caused by the c.330+1del variant in the index case from Family 8 (red box). Note absence of *AGR2* transcripts caused by the large homozygous deletion in *AGR2* in the index case of Family 6 (red box).



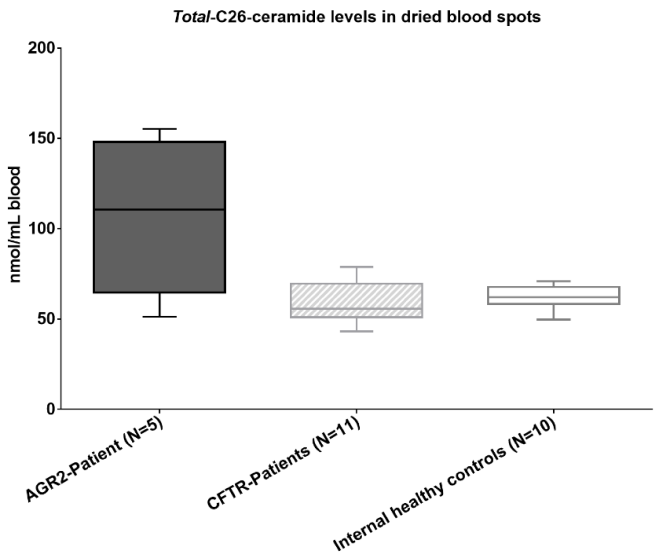
**Supplementary Figure 3:** Blood Cis, Trans and Total-Cer26 are significantly elevated in *AGR2* patients compared to healthy controls and *CFTR*-patients. ANOVA test Cis-Cer26 F=4.13, P=0.03; Trans-Cer26=4.75, P=0.02; Trans-Cer26 F=10.94, P<0.001.




| | AGR2-Patients (N=5) | CFTR-Patients (N=11) | Healthy controls (N=10) |
|---|---|---|---|
| Number of values | 5 | 11 | 10 |
| Minimum | 16.60 | 9.210 | 12.80 |
| 25% Percentile | 18.50 | 11.40 | 15.43 |
| Median | 29.70 | 14.40 | 18.10 |
| 75% Percentile | 69.95 | 22.20 | 20.78 |
| Maximum | 109.0 | 27.50 | 26.70 |
| Mean | 41.32 | 16.77 | 18.46 |
| Std. Deviation | 38.32 | 6.010 | 4.043 |
| Std. Error of Mean | 17.14 | 1.812 | 1.278 |
| Lower 95% CI of mean | -6.257 | 12.74 | 15.57 |
| Upper 95% CI of mean | 88.90 | 20.81 | 21.35 |




| | AGR2-Patient (N=5) | CFTR-Patients (N=11) | Healthy controls (N=10) |
|---|---|---|---|
| Number of values | 5 | 11 | 10 |
| Minimum | 34.70 | 22.40 | 34.20 |
| 25% Percentile | 40.50 | 37.20 | 39.90 |
| Median | 57.70 | 41.30 | 42.80 |
| 75% Percentile | 95.45 | 51.80 | 47.40 |
| Maximum | 110.0 | 56.70 | 55.30 |
| Mean | 65.92 | 42.77 | 43.74 |
| Std. Deviation | 29.98 | 10.62 | 5.939 |
| Std. Error of Mean | 13.41 | 3.203 | 1.878 |
| Lower 95% CI of mean | 28.70 | 35.64 | 39.49 |
| Upper 95% CI of mean | 103.1 | 49.91 | 47.99 |




| | AGR2-Patient (N=5) | CFTR-Patients (N=11) | Internal healthy controls (N=10) |
|---|---|---|---|
| Number of values | 5 | 11 | 10 |
| Minimum | 51.30 | 43.10 | 49.80 |
| 25% Percentile | 64.70 | 50.90 | 58.20 |
| Median | 110.6 | 55.70 | 62.05 |
| 75% Percentile | 148.1 | 69.60 | 67.65 |
| Maximum | 155.3 | 78.90 | 71.00 |
| Mean | 107.2 | 59.55 | 62.20 |
| Std. Deviation | 43.11 | 11.76 | 6.442 |
| Std. Error of Mean | 19.28 | 3.546 | 2.037 |
| Lower 95% CI of mean | 53.72 | 51.64 | 57.59 |
| Upper 95% CI of mean | 160.8 | 67.45 | 66.81 |

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