## Congenital Ichthyosis XomeDxSlice: Genes, disorders, and diagnostic yield

| Gene | Disorder | Inheritance | OMIM | Clinical sensitivity | References |
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| ABCA12 | Harlequin Ichthyosis, Autosomal Recessive Congenital Ichthyosis (ARCI) | Autosomal Recessive | #242500, #601277 | >95% Harlequin ichthyosis; 5% of all ARCI | Fischer et al. (2009) J Invest Derm 129:1319-1321. |
| ABHD5 | Chanarin-Dorfman Syndrome | Autosomal Recessive | #275630 | >95% | Lefevre et al. (2001) Am J Hum Genet 69:1002-1012; Bruno et al. (2008) Biochem Biophys Res Commun. 369(4):1125-8; Emre et al. (2010) Eur J Med Genet 53:141-144. |
| AGPS | Chondrodysplasia Punctata | Autosomal Recessive | #600121 | Rare | Itzkovitz et al. (2012) Hum Mutat. 33(1):189-97. |
| ALDH3A2 | Sjogren-Larssen Syndrome | Autosomal Recessive | #270200 | Close to 100%; Common Swedish founder mutation in Northern European individuals, common 6kb deletion including exon 9 in 28% of disease alleles in German patients. | Rizzo and Carney (2005) Hum Mut 26(1): 1-10. |
| ALOX12B | Autosomal Recessive Congenital Ichthyosis | Autosomal Recessive | #242100 | 12% of all ARCI; 7% of TGM1 negative patients | Jobard et al. (2002) Hum Mol Genet 11:107-11; Eckl et al. (2005) Hum Mut 26:351-61; Fischer et al. (2009) J Invest Derm 129:1319-1321; Eckl et al. (2009) J Invest Derm 129: 1421-1428. |
| ALOXE3 | Autosomal Recessive Congenital Ichthyosis | Autosomal Recessive | #606545 | 5% of all ARCI; 7% of TGM1 negative patients | Jobard et al. (2002) Hum Mol Genet 11:107-11; Eckl et al. (2005) Hum Mut 26:351-61; Fischer et al. (2009) J Invest Derm 129:1319-1321; Eckl et al. (2009) J Invest Derm 129: 1421-1428. |
| AP1S1 | MEDNIK Syndrome | Autosomal Recessive | #609313 | Rare; French-Canadian families | Montpetit et al. (2008) PLoS Genet 4: e1000296, 2008. Note: Electronic Article; Saba et al. (2005) Hum Genet 116: 167-171, 2005. |
| ARSE | Chondrodysplasia Punctata | X-linked Recessive | #302950 | 60- 75% in affected males, slightly lower in affected females (if assay does not include del/dup testing). Deletions occur in up to 15% of cases. | Brunetti-Pierri et al. (2003) Am J Med Genet 117A:164-168; Sheffield et al. (1998) J Med Genet 35:1004-1008; Franco et al. (1995) Cell 81:15-25. |
| CERS3 | Autosomal Recessive Congenital Ichthyosis | Autosomal Recessive | #615023 | Rare, may be part of a rare contiguous gene deletion syndrome including CERS3 and ADAMTS17 | Eckl et al. (2005) Hum Mutat 26: 351-361, 2005; Eckl et al. (2013) J Invest Derm 133: 2202-2211. |
| CLDN1 | NISCH Syndrome | Autosomal Recessive | #607626 | Rare | Hadj-Rabia et al. (2005) Gastroenterology 127: 1386-1390; Feldmeyer et al. (2006) Hum Mutat 27: 408-410. |
| CYP4F22 | Autosomal Recessive Congenital Ichthyosis | Autosomal Recessive | #604777 | Uncommon; in one study up to 8% of all ARCI | Lefevre et al. (2006) Hum Mol Genet 15:767-776; Fischer et al. (2009) J Invest Derm 129:1319-1321. |
| EBP | Chondrodysplasia Punctata-2; CHILD syndrome | X-linked | #302960 | Up to 85% of females with suspected CDPX2 and 91% in females with abnormal sterol profile | Has et al. (2000) Hum Mol Genet 13:1951–1955; Braverman et al. (1999) Nat Genet 22:291–294; Ikegawa et al. (2000) Am J Med Genet 94:300–305; Herman et al. (2002) Genet Med 4: 434-438. |
| ELOVL4 | Ichthyosis, Spas | Autosomal Recessive | #614457 | Rare, only 1 report published | Aldahmesh et al. (2011) Am J Hum Genet 89: 745-750. |
| FLG | Ichthyosis Vulgaris | Autosomal Semi-dominant | #146700 | 80 - 90% in individuals of North or West-European decent | Thyssen et al. (2013) The British Journal Of Dermatology 168 (6):1155-66. |
| GJB2 | KID Syndrome, Palmoplantar Keratoderma with SNHL | Autosomal Dominant | #148210, #148350 | >90% in KIDS; p.D50N accounts for ≈ 80% of mutations. Sensitivity for pts with PPK/SNHL is unknown | KIDS: Richard et al. (2002) Am J Hum Genet 70:1341-1348; van Steensel et al. (2002) J Invest Dermatol 118:724-727; PPK: Richard (2005) Clinics in Dermatology, 23:23-32; Maestrini et al. (1999) Hum Mol Genet 8:1237–1243; Richard et al. (2004) J Invest Dermatol 123(5):856-63. |
| GJB3 | Erythrokeratoderma Variabilis | Autosomal Dominant/Autosomal Recessive | #133200 | ≈ 66%; 57% of the mutations were found in the GJB3 gene and the remaining 43% in the GJB4 gene. Rarely, families with autosomal recessive EKV have been reported. | Richard et al. (1998) Nat Genet 20:366-369; Richard et al. (2000) Hum Genet 106:321-329; Macari et al. (2000) Am J Hum Genet 67:1296-1301; Gottfried et al. (2002) Hum Mol Genet 11:1311-1316; Richard et al. (2003) J Invest Dermatol 120:601-609; Terrinoni et al. (2004) J Invest Dermatol 122:837-839; Common et al. (2005) J Invest Dermatol 125:920-927. |
| GJB4 | Erythrokeratoderma Variabilis | Autosomal Dominant/Autosomal Recessive | #133200 | | |
| GJB6 | Clouston Syndrome, KID Syndrome | Autosomal Dominant | #129500 | >95% of Clouston syndrome/HED; very rare in KIDS | Lamartine et al. (2000) Nat Genet 26(2):142-4; van Steensel et al. (2003) J Invest Dermatol 121(5):1035-8; Smith et al. (2002) J Invest Dermatol 118(3):530-2; Jan et al. (2004) J Invest Dermatol 122(5):1108-13. |

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| KRT1 | Epidermolytic Ichthyosis, Palmoplantar Keratoderma | Autosomal Dominant | #113800, #146590, #607602, #607654, #144200, #600962 | >80% of EI, about 50% of mutations occur de novo. >90% of mutations cluster at mutational "hot spots" at helix initiation and termination motifs of the rod domains. Sensitivity in epidermolytic and non-epidermolytic PPK is unknown | Irvine and McLean. (1999) Br J Dermatol 140:815-828; Corden and McLean (1996) Exp Dermatol 5:297–307; Szeverenyi et al. (2008) Hum Mutat 29(3):351-360. |
| KRT10 | Epidermolytic Ichthyosis | Autosomal Dominant | #113800, #609165, #607602 | | |
| KRT2 | Superficial Epidermolytic Ichthyosis | Autosomal Dominant | #146800 | >80% | Irvine and McLean. (1999) Br J Dermatol 140:815-828. |
| KRT9 | Epidermolytic Palmoplantar Keratoderma | Autosomal Dominant | #144200 | rare, unknown | Alsaleh and Teebi. (1990) J Med Genet 27: 519-522. |
| LIPN | Autosomal Recessive Congenital Ichthyosis | Autosomal Recessive | #613943 | Rare; only 1 report published | Israeli et al. (2011) Am J Hum Genet 88: 482-487; Lefevre et al. (2006) Hum Molec Genet 15: 767-776. |
| LOR | Loricrin Keratoderma | Autosomal Dominant | #604117 | Rare | Ishida-Yamamoto et al. (1997) Am J Hum Genet 61: 581-589; Maestrini et al. (1996) Nature Genet 13: 70-77. |
| NIPAL4 | Autosomal Recessive Congenital Ichthyosis | Autosomal Recessive | #612281 | Up to 16% of all ARCI in one study, likely less in other populations | Lefevre et al. (2004) Hum Mol Genet 13:2473-2482; Dahlqvist et al. (2007) J Med Genet 44: 615- 620; Fischer et al. (2009) J Invest Derm. 129:1319-1321. |
| PEX7 | Refsum Disease | Autosomal Recessive | #614879 | <10% | Van den Brink et al. (2003) Am J Hum Genet 72:471–477. |
| PHYH | Refsum Disease | Autosomal Recessive | #266500 | >90% | Mihalik et al. (1997) Nat Genet 17:185–189; Jansen et al. (1999) Adv Exp Med Biol 466:371–376. |
| PNPLA1 | Autosomal Recessive Congenital Ichthyosis | Autosomal Recessive | #615024 | Rare; only 1 report published | Grall et al. (2012) Nature Genet 44: 140-147. |
| PNPLA2 | Neutral Lipid Storage Disease with Myopathy | Autosomal Recessive | #610717 | Rare | Fischer et al. (2007) Nature Genet 39: 28-30; Reilich et al. (2011) J Neurol 258: 1987-1997; Lin et al. (2012) J Hum Genet 57: 679-681. |
| POMP | Keratosis Linearis with Ichthyosis Congenita and Sclerosing Keratoderma | Autosomal Recessive | #601952 | Rare; only 1 report published | Dahlqvist et al. (2010) Am J Hum Genet 86: 596-603. |
| SLC27A4 | Ichthyosis Prematurity Syndrome | Autosomal Recessive | #608649 | close to 100%, especially in pts of Scandinavian descent. | Klar et al (2009) Am J Hum Genet 85:248-253; Sobol et al (2011) BMC Research Notes 4:90. |
| SNAP29 | CEDNIK Syndrome | Autosomal Recessive | #609528 | Rare | Fuchs-Telem et al. (2011) Brit J Derm 164: 610-616; Sprecher et al. (2005) Am J Hum Genet 77: 242-251. |
| SPINK5 | Netherton Syndrome | Autosomal Recessive | #256500 | 66-75% | Richard et al. (2004) J Invest Dermatol 122:483A. |
| ST14 | Autosomal Recessive Congenital Ichthyosis with Hypotrichosis | Autosomal Recessive | #602400 | Rare | Avrahami et al. (2008) Clin Genet 74: 47-53; Basel-Vanagaite et al. (2007) Am J Hum Genet 80: 467-477. |
| STS | Steroid Sulfatase Deficiency | X-linked Recessive | #308100 | ≈85-90% of pts with X-linked ichthyosis have a genomic deletion including the STS gene and flanking sequences; the remainder have mutations identifiable by sequencing | Valdes-Flores et al. (2000) J Invest Dermatol 114(3):591-3; Oyama et al. (2000) J Invest Dermatol 114:1195–1199; Shapiro et al. (1989) Proc Natl Acad Sci U S A 86:8477-81; Alperin and Shapiro. (1997) J Biol Chem 272:20756-63; Canueto et al. (2010) J Eur Acad Dermatol Venereol 24:1226-9. |
| TGM1 | Lamellar Ichthyosis, Autosomal Recessive Congenital Ichthyosis | Autosomal Recessive | #242300 | >90% LI; 32-55% of all ARCI | Fischer et al. (2009) J Invest Derm 129:1319-1321; Eckl et al. (2009) J Invest Derm 129: 1421-1428; Herman et al. (2009) Hum Mutat 30:537-47; Farasat et al. (2009) J Med Genet 46(2):103-11. |
| TGM5 | Acral Peeling Skin Syndrome | Autosomal Recessive | #609796 | Rare | Cassidy et al. (2005) Am J Hum Genet 77: 909-917; Hashimoto et al. (2000) J Am Acad Derm 43: 1112-1119; Pigors et al. (2012) J Invest Dermatol 132(10):2422-9. |
| VPS33B | Arthrogryposis-Renal Dysfunction-Cholestasis Syndrom-1 | Autosomal Recessive | #208085 | In one study, 77% of patients and 80% of families had mutations | Gissen et al. (2006) Hum Genet 120: 396-409; Smith et al. (2012) Hum Mutat 33:1656-1664. |

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| ZMPSTE24 | Restrictive Dermopathy | Autosomal Recessive | #275210 | Rare; less than 50 cases reported worldwide; common in Schmiedeleut Hutterites in the United States, with carrier frequency 1 in 15.5. | Chong et al. (2012) Am J Hum Genet 91:608-620; Loucks et al. (2012) Am J Med Genet 158A:1229-1232; Moulson et al. (2005) J Invest Derm 125:913-919. |