Genetic evaluation of the patients with clinically diagnosed inborn errors of immunity by whole exome sequencing: Results from a specialized research center for immunodeficiency in Türkiye

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Supplementary Table 1: Detailed evaluation of possible disease-causing monoallelic variants

Patient no	Gene	Variant	CADD	ACMG criteria	Associated features	Novelty	Reporting status	Functional demonstration
P19	*SAMD9L*	c.A2639C p.His880Pro	27.6	VUS	Dandy Walker malformation, low B cells	Novel	-	Aplastic anemia in bone marrow examination
P42	*CTLA4*	c.118G>A p.Val40Met	24.3	VUS	AIHA, enteropathy, reduced T and B cells	rs1553657378	[1-4]	-
P43	*JAK1*	c.2485A>G p.Asn829Asp	23.7	VUS	IBD, lymphopenia, vitiligo	Novel	-	Increased phosphorylation of JAK1 and STAT1
P53	*ELANE*	c.703delG p.Val235TrpfsTer5	-	VUS	Recurrent bacterial infections, severe congenital neutropenia	Novel	-	Congenital neutropenia
P54	*HCK*	c.135_136delinsTG p.Pro46Ala	-	VUS	Nodulocystic acnes, cutaneous vasculitis, HSM	Novel	-	Increased phosphorylation of STAT5, high levels of inflammatory cytokines
P70	*FAS*	c.361C>T p.Arg121Trp	22.1	Pathogenic/ Likely Pathogenic	Splenomegaly, lymphadenopathy, ITP	rs121913078	[5]	-
P74	*CTLA4*	c.151C>T p.Arg51Ter	34	Pathogenic	Lymphadenopathy, lymphopenia, hypogammaglobulinemia, reduced switched memory B cells	rs606231417	[4, 6]	-
P82	*ELANE*	c.367-8C>A	-	VUS	Early onset IBD, oral aphtosis, recurrent gastrointestinal infections, severe congenital neutropenia	novel	-	Reduced/absence expression of ELANE by western blot
P85	*FAS*	c.772A>AG p.Lys258Glu	23.6	VUS	Lymphoproliferation, elevated DNT	novel	-	Aberrant lymphocyte apoptosis
P88	*BACH2*	c.745del p.Ser249ValfsTer93	-	Likely Pathogenic	IBD, pancreatitis, hypogammaglobulinemia	novel	-	Reduced/absence expression of BACH2 by western blot
P93	*CHD7*	c.1904A>T p.Asp635Val	27	VUS	Facial dismorphic features, recurrent pulmonary infections, chronic severe diarrhea, reduced CD3 lymphocytes	rs752468864	-	Poor proliferative T cell response, fulfilling criteria for CHARGE syndrome [7]
P96	*TBK1*	c.1055T>C p.Leu352Pro	26.1	VUS	Enteroviral meningitis, recurrent sinopulmonary infections, failure to thrive	novel	-	Impaired immune response to TLR3-dependent viruses
P101	*PIK3CD*	c.1573G>A p.Glu525Lys	24.8	Pathogenic/ Likely Pathogenic	Lichen planus, fulminant hepatic failuire, granuloma, ITP,	rs587777389	[8, 9]	-

					lymphoproliferation, reduced switched memory B cells			
P102	*FAS*	c.340G>A p.Glu114Lys	26.5	VUS	Missense	rs773565107	-	Aberrant lymphocyte apoptosis
P103	*STAT1*	c.1192G>A p.Gly397Ser	28.9	VUS	Recurrent pulmonary infections, bronchiectasis, CMC, nail dystrophia, severe growth retardation, hypothyroidism, hypergammaglobulinemia, CD4+ T cel lymphopenia	novel	-	
P104	*IL6ST*	c.2093C>A p.Ala698Glu	23.3	VUS	Recurrent pulmonary infections, bronchiectasis, severe eczema, hypogammaglobulinemia, elevated IgE, lymphopenia	rs745818447	-	
P122	*PIK3CD*	c.1573G>A p.Glu525Lys	29.6	Pathogenic/ Likely Pathogenic	EBV infection, lymphadenopathy, reduced IgA and IgG	rs587777389	[8, 9]	-

CADD: Combined Annotation Dependent Depletion ACMG: American College of Medical Genetics and Genomics VUS: Variant of Uncertain Significance AIHA: Autoimmune hemolytic anemia HSM: Hepatosplenomegaly IBD: Inflammatory bowel disease ITP: Immune thrombocytopenic purpura DNT: Double negative T cells

References

1. Egg D, Rump IC, Mitsuiki N, Rojas-Restrepo J, Maccari ME, Schwab C, et al. Therapeutic options for CTLA-4 insufficiency. J Allergy Clin Immunol. 2022;149(2):736-46.
2. Hoshino A, Tanita K, Kanda K, Imadome KI, Shikama Y, Yasumi T, et al. High frequencies of asymptomatic Epstein-Barr virus viremia in affected and unaffected individuals with CTLA4 mutations. Clin Immunol. 2018;195:45-8.
3. Rae W, Ward D, Mattocks C, Pengelly RJ, Eren E, Patel SV, et al. Clinical efficacy of a next-generation sequencing gene panel for primary immunodeficiency diagnostics. Clin Genet. 2018;93(3):647-55.
4. Schwab C, Gabrysch A, Olbrich P, Patino V, Warnatz K, Wolff D, et al. Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects. J Allergy Clin Immunol. 2018;142(6):1932-46.
5. Bettinardi A, Brugnoni D, Quiros-Roldan E, Malagoli A, La Grutta S, Correra A, Notarangelo LD. Missense mutations in the Fas gene resulting in autoimmune lymphoproliferative syndrome: a molecular and immunological analysis. Blood. 1997;89(3):902-9.
6. Kuehn HS, Ouyang W, Lo B, Deenick EK, Niemela JE, Avery DT, et al. Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4. Science. 2014;345(6204):1623-7.

7. Verloes A. Updated diagnostic criteria for CHARGE syndrome: a proposal. Am J Med Genet A. 2005;133A(3):306-8.
8. Coulter TI, Chandra A, Bacon CM, Babar J, Curtis J, Screaton N, et al. Clinical spectrum and features of activated phosphoinositide 3-kinase delta syndrome: A large patient cohort study. J Allergy Clin Immunol. 2017;139(2):597-606 e4.
9. Lucas CL, Kuehn HS, Zhao F, Niemela JE, Deenick EK, Palendira U, et al. Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110delta result in T cell senescence and human immunodeficiency. Nat Immunol. 2014;15(1):88-97.