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Pulmogenetics-**XVIII**/ Syndromes associated with Bronchiectasis / Polycystic lung disease (PLD)

Author: Prashant Kumar Verma[1], Manmeet Singh Khalsa[2]

[1]Chairperson of Medical Genetic division, [2]Senior Resident in Pediatric pulmonology division, department of Pediatrics, AIIMS Rishikesh, Uttarakhand, India

Reviewer: Dr. Raksha Ranjan[1]

[1]Department of Pediatrics, AIIMS Bathinda, Punjab, India

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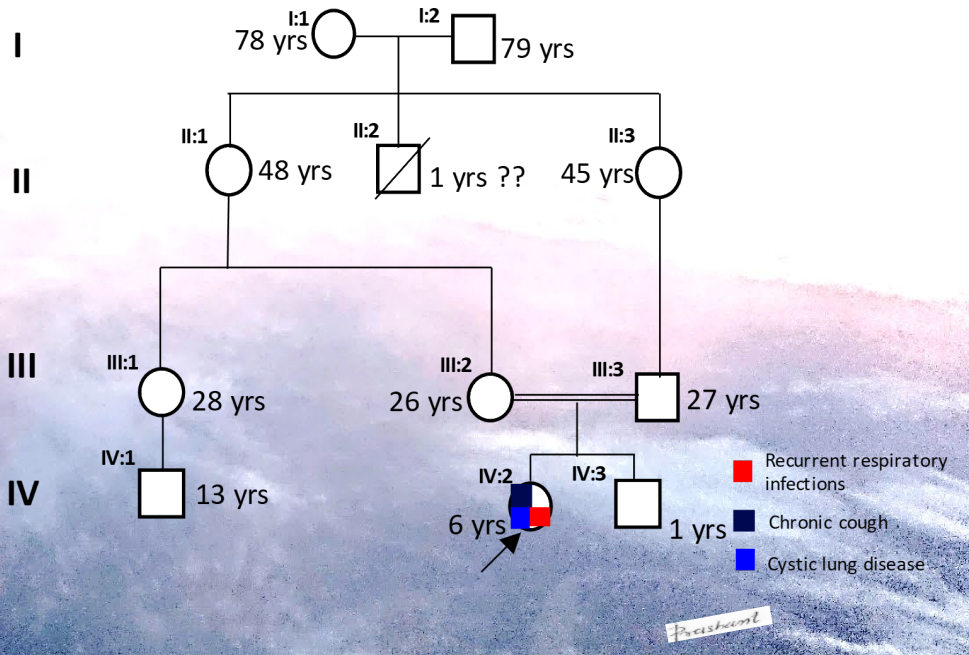
From the desk of Editor

The Genetic Division of the Pediatric Department publishes a monthly newsletter for all medical professionals. The newsletter pertains to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.



Insight:

1. What is the age-wise clinical presentation and radiological evolution of CCR2 related PLD?
2. What is CRISPR?
3. Is there any relationship between radiological and clinical phenotype?
4. What is molecular mechanism for CCR2 related PLD?
5. How would you approach a neonate presenting with BCG-related disease, including BCGosis and BCGitis?
6. Is there any need to perform a molecular test in asymptomatic case IV:3?

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)

- It is an adaptive immune system in bacteria and archaea. Cas9 is an **RNA-guided DNA endonuclease**.
- A programmable single-guide RNA (**sgRNA**) directs Cas9 to a complementary DNA sequence
- CRISPR-associated protein 9 (**Cas9**) recognizes a target **adjacent to a Protospacer Adjacent Motif (PAM) sequence** and generates a DNA double-strand break
- Basic principle of CRISPR-Cas gene-editing systems: sgRNA + Cas9 → Target DNA recognition → DNA cleavage → Cellular DNA repair.
    - Non-Homologous End Joining (NHEJ) → insertions/deletions (indels) → gene disruption / CRISPR knockout
    - Homology-Directed Repair (HDR) + donor template → precise sequence replacement or insertion
- **How CRISPR transformed genetics:** Sequence-specific, programmable, multiplexable, and applicable to many cell lines.

CRISPR Toolkit: From Gene Editing to Gene Regulation

CRISPR approach	Molecular strategy	Main application
CRISPR-KO	Cas9 cleavage → NHEJ/indels	Permanent gene disruption
CRISPRi	dCas9 + repressor → transcriptional repression	Reversible/graded gene depletion
CRISPRa	dCas9 + activator → transcriptional activation	Gene overexpression
Base editing	Catalytically modified Cas + deaminase	Precise single-base changes
Prime editing	Cas nickase + reverse transcriptase	Precise sequence editing

Mendelian disorders/genes have documented disseminated BCG disease after BCG vaccination

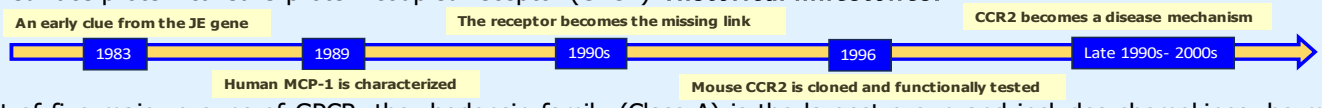
In OMIM, we retrieve 26 entries by searching ((disseminated AND BCG AND disease)); only nineteen entries have been selected on the basis of strong evidence based publications.

Disease / OMIM no.	Gene / MOI	Gene function	Key BCG-related features	Additional features	PMID
Immunodeficiency 88 / OMIM #619630	TBX21 / AR	T-bet; drives Th1 differentiation and IFN-γ production.	Disseminated mycobacterial disease after BCG; impaired IFN-γ production.	Reactive airway disease; impaired Th1 responses; susceptibility to other intracellular pathogens may occur.	33296702
Immunodeficiency 31B + 31A / OMIM #613796 + #614892	STAT1 / AR complete LOF; AD partial LOF	Major transcription factor for IFN-γ and type-I IFN signalling.	Disseminated BCG; BCG osteomyelitis and other severe mycobacterial disease.	Complete deficiency: severe early-onset infections. AD partial deficiency: later-onset/recurrent mycobacterial infections; susceptibility to viral/fungal infections can occur.	36349275; 37516851
Immunodeficiency 32B + 32A / OMIM #226990 + #614893	IRF8 / AR; AD partial LOF	Controls monocyte/macrophage and dendritic-cell development and IL-12/IFN-γ immunity.	Disseminated BCG, particularly in complete AR deficiency.	Monocytopenia; dendritic-cell deficiency; impaired NK-cell/Th1 responses; susceptibility to other intracellular pathogens.	35338423
Immunodeficiency 33 / OMIM #300636	IKBKG/NEMO / X-linked	IKK-complex component required for NF-κB activation.	Disseminated BCG/BCG-osis and other atypical mycobacterial infections.	Ectodermal dysplasia in many patients; recurrent bacterial infections; susceptibility to pneumococcus, mycobacteria and viruses; inflammatory manifestations.	21755389; 27470647
Immunodeficiency 27A + 27B / OMIM #209950 + #615978	IFNGR1 / AR complete; AD partial	IFN-γ receptor chain 1; initiates IFN-γ–JAK/STAT1 signalling.	Complete deficiency: severe early disseminated BCG. Partial AD deficiency: recurrent BCG/NTM disease.	Salmonella and other intracellular infections; osteomyelitis; lymphadenitis; granulomatous disease.	8960475
Immunodeficiency 28 / OMIM #614889	IFNGR2 / AR	IFN-γ receptor chain 2; required for IFN-γ signalling.	Severe disseminated mycobacterial/BCG disease.	Salmonellosis and other intracellular infections; high circulating IFN-γ with absent cellular response in complete receptor deficiency.	31497017
Immunodeficiency 29 / OMIM #614890	IL12B / AR	IL-12/IL-23 p40 subunit; promotes IFN-γ production.	Disseminated BCG is a characteristic presentation.	Salmonella and other intracellular bacterial infections; generally, relatively preserved immunity; some patients develop mucocutaneous Candida.	12591909
Immunodeficiency 30 /OMIM #614891	IL12RB1 / AR	Shared IL-12/IL-23 receptor chain.	Recurrent/disseminated BCG disease.	Salmonellosis; other NTM infections; mucocutaneous candidiasis; variable severity and age of onset.	24863105; 29025965; 41668770
Immunodeficiency 69 / OMIM #618963	IFNG / AR	Encodes IFN-γ, the principal macrophage-activating cytokine against intracellular microbes.	Disseminated BCG/mycobacterial infection.	Fever, hepatosplenomegaly, lymphadenopathy, leukocytosis and thrombocytosis; otherwise relatively preserved adaptive immunity.	32163377
CGD3 / OMIM #613960	NCF4/p40phox /AR	NADPH oxidase component required for phagocyte ROS generation.	BCG-itis/BCG-related disease reported; attribution should be interpreted cautiously when other variants coexist.	Recurrent bacterial and fungal infections; granuloma formation; inflammatory complications characteristic of CGD spectrum.	29969437
Immunodeficiency 35 / OMIM #611521	TYK2 / AR	JAK-family kinase integrating IL-12/IL-23 and type-I IFN signalling.	Disseminated BCG infection/BCG-osis.	Susceptibility to other intracellular bacteria, Salmonella, viruses and fungi; variable severity depending on variant.	22402565; 36094518; 41465118
Immunodeficiency 118 / OMIM #301115	MCTS1 / X-linked recessive	Translation-reinitiation factor required for efficient JAK2 translation and IL-23–IFN-γ signalling.	BCG-osis, including disseminated BCG, in affected males.	Impaired IL-23/IFN-γ axis; recurrent mycobacterial disease; variable involvement of lung, liver, CNS and gastrointestinal tract.	37875108; 41623352
Immunodeficiency 42 / OMIM #616622	RORC/RORγ / AR	Controls RORγt-dependent Th17/IL-17/IL-22 immunity and antimicrobial T-cell programs.	Disseminated BCG and other mycobacterial disease.	Chronic mucocutaneous candidiasis; impaired IL-17 responses; altered MAIT/innate-like T-cell compartments.	26160376
Immunodeficiency 91 and hyperinflammation / OMIM #619644	ZNFX1 / AR	Nucleic-acid/RNA sensor involved in innate immune antiviral and inflammatory responses.	Disseminated BCG/mycobacterial disease reported.	Recurrent viral infections; hyperinflammation; lymphadenopathy; hepatosplenomegaly; hepatitis/hepatic failure; renal and neurologic involvement; potentially fatal multiorgan inflammation.	33876776
Immunodeficiency 112 / OMIM #620449	MAP3K14/NIK / AR	Central kinase of the noncanonical NF-κB pathway.	Disseminated BCG-osis reported.	Variable combined immunodeficiency; recurrent bacterial, viral and fungal infections; hypogammaglobulinemia; abnormal B-cell/lymphocyte compartments.	29230214; 34093558
Immunodeficiency 117 / OMIM #620668	IRF1 / AR	IFN-γ-responsive transcription factor regulating antimicrobial and IL-12/IFN-γ pathways.	Disseminated BCG after vaccination.	Defective myeloid-cell development/function; impaired IFN-γ production/response; susceptibility to M. avium and other intracellular bacteria.	36736301
Polycystic lung disease / OMIM #219600	CCR2 / AR	CCL2 receptor controlling monocyte recruitment and macrophage trafficking.	BCG lymphadenitis and disseminated BCG reported.	Progressive polycystic lung disease; pulmonary alveolar proteinosis; recurrent respiratory infections; abnormal monocyte/macrophage trafficking.	38157855
Omenn syndrome / OMIM #603554	RAG1, RAG2, DCLRE1C / AR	RAG1/RAG2 initiate V(D)J recombination; DCLRE1C/Artemis repairs DNA ends.	BCG infection including disseminated BCG can occur as a complication of severe SCID/Omenn phenotype.	Generalized erythroderma/rash; eosinophilia; very high IgE; lymphadenopathy; hepatosplenomegaly; severe viral, bacterial and fungal infections; profound T-cell dysfunction.	1915499; 34406419
Immunodeficiency 76 / OMIM #619164	FCHO1 / AR	Endocytic protein involved in clathrin-mediated endocytosis and TCR internalization.	BCG-site abscess/BCG-itis with regional lymphadenopathy reported.	T-cell lymphopenia; recurrent bacterial, viral and fungal infections; variable B-cell/Ig abnormalities; neurologic manifestations and lymphoma have been described.	30822429; 39498505

Plausible tenets:

Gene: CCR2 (Chemokine, CC Motif, Receptor 2); 3p21.31, genomic coordinates (GRCh38): 3:46,354,111-46,360,940

- Its product belongs to rhodopsin family (Class A) of a large superfamily of a seven-transmembrane receptors (**7TM receptors**),a cell surface protein called G-protein-coupled receptor (GPCR). ***Historical milestones:***



- Out of five major groups of GPCR, the rhodopsin family (Class A) is the largest group and includes chemokines, hormones, neurotransmitters, and sensory signaling. Its protein functions like chemokine receptor, and regulates immune-cell migration, especially the recruitment of monocytes to sites of inflammation.
- Its discovery helps to understand how inflammation can contribute to cardiovascular disease, utility of knockout mice in gene discovery, new pathways for targeted anti-inflammatory medicines, and a possible connection between inflammation and cancer.
- **Molecular pathology:** Injured, infected, or inflamed tissue → releases chemokines such as CCL2/MCP-1 → CCL2 binds to CCR2 → activating signaling in CCR2-expressing immune cells → immune-cell migration **monocytes** move toward the chemokine source and can enter affected tissue → **coordinate defense and tissue responses, +/- chronic disease → loss-of-function mutation of CCR2→ leads to following consequences at cellular level:**
  - **Impaired Signalling:** monocytes fail to recruit to the lungs
  - **Fewer monocytes reach the lungs:** decreased monocyte-derived alveolar macrophages (Mo-AMs)
  - **Left only tissue-resident alveolar macrophages (TR-AMs):** alveolar macrophage numbers decrease
  - **Insufficient alveolar macrophage:** dysfunction of surfactant clearance (**pulmonary alveolar proteinosis**), and lymphocyte accumulation around small airways, peribronchiolar inflammation, and some surrounding fibrosis
  - **Small airways become narrowed:** air trapping and **progressive cyst formation** (**a check-valve effect**)
- **Gene:** Size 6.83 kb, number of 144 orthologs, 23 paralogs, and 5 splice variants.
- Transcript: Total 2 exons & 2 coding exons; transcript length 2,671 bp.
- Protein: Number of 374 AA with a molecular mass of 42 kDa.
- CCR2 is expressed in monocytes, macrophage-lineage cells, and selected immune-cell subsets.

Phenotype: Polycystic lung disease (AR), and {HIV infection, susceptibility/resistance to}

- **Mutation spectrum and genotype–phenotype relationship:** Rare biallelic loss-of-function variants & **p.Thr21Profs*18** associated with cystic lung disease, **p.Leu215Pro** linked to progressive respiratory dysfunction, and **Val64Ile (rs1799864)** associated with modified HIV-1 progression rates and coronary calcification profiles across specific genotypes.
- **Management:**There is no CCR2-specific targeted therapy. Treatment is focused on clinical manifestations and be individualized according to disease severity.

***MCP-1 R (monocyte chemoattractant protein-1 receptor)]**

Clinico-radiological discordance in PLD (PMID 40432300)

Phenotype	Clinical	Radiological (HRCT)
Mild	Asymptomatic or mild exertional dyspnea/cough; preserved growth	May have moderate/extensive cystic disease despite few symptoms
Moderate	Persistent cough, exertional dyspnea, RTI, exercise intolerance; mild–moderate airflow obstruction	Usually established multicystic disease, but cyst burden does not necessarily predict symptom severity or LFT
Severe	Marked exertional dyspnea, significant airflow obstruction, recurrent/severe infections, growth failure, clubbing, hypoxemia, and substantial functional limitation	May have extensive cystic lung disease, PAP/parenchymal abnormalities and fibrosis; however, radiological extent can remain relatively stable while pulmonary function continues to deteriorate

Molecular testing in case IV: 3 – Yes, molecular testing is recommended, even in asymptomatic cases**, and i**rrespective of mode of inheritance, if molecular testing will alter the management plan or improve clinical outcomes in patient care.
Asymptomatic PLD cases need individualized care and should follow the preventive measures and long-term surveillance.

Age wise Clinical Presentations (PMID: 38157855)

Typical Age / Timing	Clinical Presentation
Infancy to 5 years approximately	May initially be asymptomatic; recurrent respiratory infections can occur
Mean 5.1 ± 3.6 years	Exertional dyspnea and/or chronic/recurrent cough are the main presenting symptoms
Approximately 4 to10 years	Progressive cystic lung disease, recurrent pneumonia/respiratory infections, exercise intolerance
Around 8 to 16 years	Increasing dyspnea, cough, obstructive lung disease; digital clubbing may develop
Variable	Progressive airflow obstruction, extensive polycystic lung disease and reduced exercise tolerance

Thought Riveting:

- *Why do lung tissues only predominantly show the phenotype of CCR2 dysfunction?*
- *Can overexpression of alternative receptors to CCR2 help in CLD management?*
- *Could pulmonary macrophage transplantation (PMT) be a game changer in the CLD management?*
- *Does CCR2 play an important role in embryonic lung development? Could subtle developmental lung abnormalities explain rapid cyst formation in CCR2-related diseases?*