UNIVERSITÄT LEIPZIG

Medizinische Fakultät

Genetic Regulation of Cytokine Response in Patients with Acute Community-Acquired Pneumonia

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Article

Genetic Regulation of Cytokine Response in Patients with Acute Community-Acquired Pneumonia

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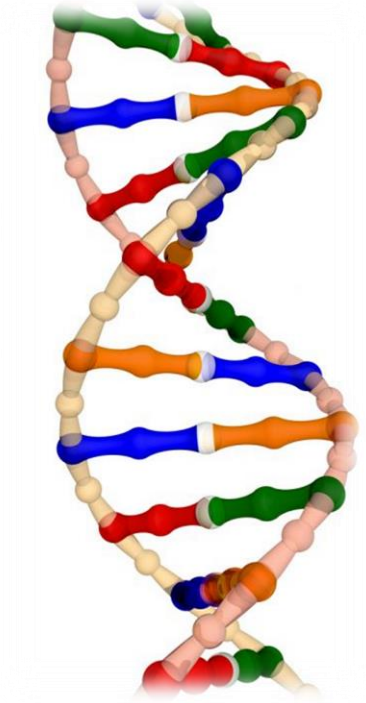
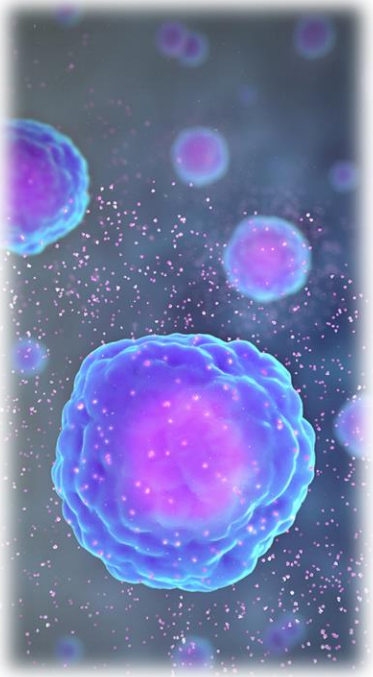
1 MOTIVATION

- Community-acquired pneumonia (CAP): acute inflammatory condition of lung with risk of **rapid deterioration** with **high mortality**
- Affects people of **all ages**
- **Hospitalisation** often required
- High inter-individual **heterogeneity** due to complex regulation of immune system with highly **non-linear dynamics**
- Cytokines released during inflammatory response shown to be **predictive for treatment failure/mortality**
- Cytokine dynamics **causally related to clinical outcome parameters** (SOFA, hematocrit, creatinine, bilirubin)
- Genetic determinants **poorly investigated** so far

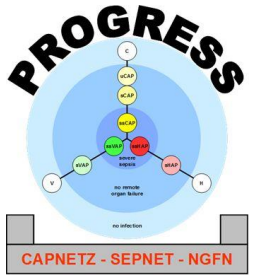
2 RESEARCH QUESTION



Which genetic determinants are associated with cytokine response of CAP patients?



3 MATERIAL: COHORT, PHENOTYPE, GENOTYPE



- PROGRESS study
- LUMINEX based multiplex Bead Array System (Luminex 200, Luminex, DiaSorin, Austin, TX, USA)
  - IL-1β, IL-6, IL-8, IL-10, IL-12, MCP-1 (MCAF), MIP-1α (CCL3), VEGF, VCAM-1, ICAM-1
  - N = 400

- CAP2 array (based on Axiom Genome-Wide CEU 1 Array Plate)
  - after QC and Imputation (IMPUTE2, 1kGP3V5):
    - N = 2,174 probands
    - M = 85,064,535 SNPs

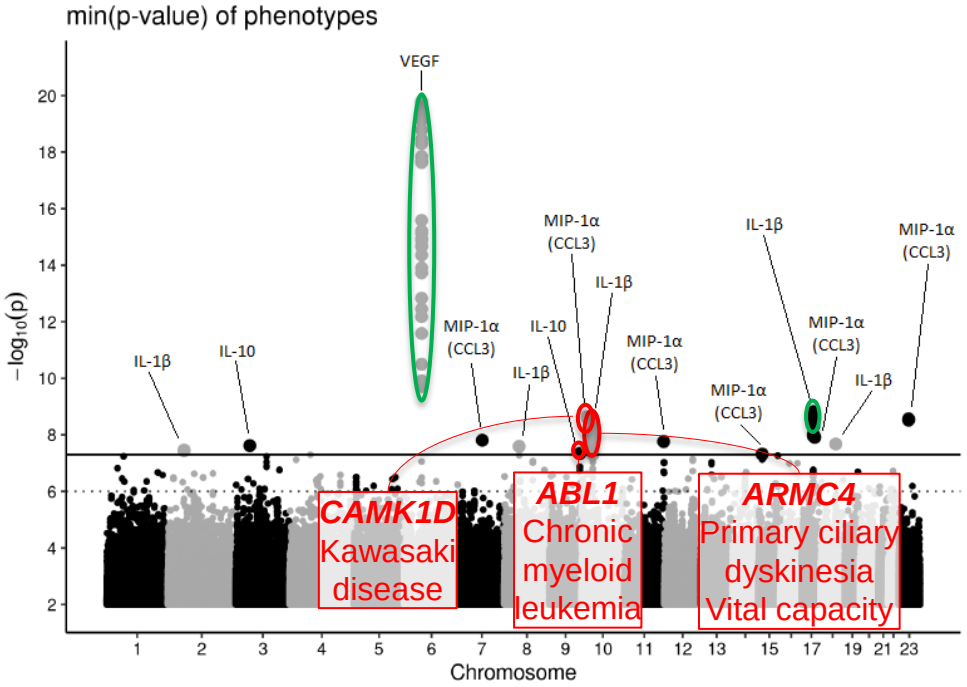
- **Phenotype & genotype data: N_{min} = 361, N_{max} = 389**

4 METHODS: STATISTICAL ANALYSIS

1. GWAS for 10 cytokines
2. Conditional and joint analysis / Credible set analysis
3. Colocalisation analysis
4. MetaXcan analysis
5. Lookup of cytokine-coding genes

5 RESULTS: 1. GWAS FOR 10 CYTOKINES (INCLUDING 2.-4.)

- **102** genome-wide significant **associations**
- distributed on **14 loci**
- **5** of ten **cytokines** involved
- $0.9934 \leq \lambda_{GC} \leq 1.0140$



2 known loci

6p21.1 (VEGF)
- 99%-CS for independent lead-SNP: 12 SNPs
- Lead-SNP colocalises with eQTL of C6orf223 in whole blood (PP=93.7%)
- Another tag-SNP with CADD-Score of 10.84
- Significant associations with C6orf223 in whole blood by MetaXcan (3 SNPs in model analysis)

17q21.32 (IL-1β)
- 99%-CS for independent lead-SNP: 23 SNPs
- Significant associations with 13 genes in all tissues except heart atrial appendage by MetaXcan (median 2 SNPs in model analysis)

3 plausible novel loci

10p12.1 (IL-1β)
- 99%-CS: 50 SNPs
- Another tag-SNP with CADD-Score of 11.04

5 RESULTS: 5. LOOKUP OF CYTOKINE-CODING GENES

- Significant associations for 40 SNPs from a total of 24,354 SNPs (hierarchical FDR ≤ 5%)
- Only 2 cytokines involved in these associations
  - 39 SNPs correspond to VEGF at locus 6p21.1
    - Multiple cancers
    - Large artery atherosclerotic stroke
  - 1 SNP corresponds to MIP-1α (CCL3) at locus 17q12
    - Acute lymphoblastic leukemia
    - Cervical cancer
    - Fraction of exhaled nitric oxide values

6 LIMITATIONS

- Individual‘s immune responses depends on various factors and are also affected by the pathogen which is known only for small subset of patients of our cohort
- Total sample size of this study was small
- Replication of our results in other cohorts required
- Cytokine response dynamics not analysed

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THANK YOU FOR YOUR ATTENTION ☺

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