

Discovering new genetic causes of auto inflammatory disease in children

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Hypothesis: Using state of the art genetic mapping and next-generation sequencing techniques, it is possible to discover novel monogenic diseases resulting in pathological inflammation.

Aims and methods:

Primary objective: Identify responsible mutations for undefined familial autoinflammatory diseases (first half of project)

Secondary objective: To further characterise the phenotype of the mutation on the patients' cells and in vitro cell culture models (second half of project).

The term autoinflammatory disease was coined just over 10 years ago following the discovery of the genetic cause of familial Mediterranean Fever (Pyrin mutation) (1), followed rapidly by the discovery of the genetic cause of another inflammatory disease called TRAPS (TNF receptor associated periodic fever syndrome, caused by mutations in the TNFR1 gene) (2). Autoinflammatory diseases are distinct from autoimmune diseases since they result in seemingly unprovoked inflammation, in the absence of autoantibodies, and without the presence of autoreactive T cells (3). Many are associated with genetic defects in the innate immune system. We are currently developing an exciting new programme of research at Great Ormond Street Hospital (GOSH) that aims to discover new genetic causes of inflammatory diseases in children. This unique opportunity is possible because of a rapidly expanding clinical service at GOSH that has been developed over the last 10 years in collaboration with the Royal Free Hospital in London: the periodic fever syndrome clinic. In the first part of project, the student will analyze affected individuals belonging to 2 (from a choice of five) consanguineous (i.e. parents first cousins) families suffering from a recessive disorder. Homozygosity mapping will be carried out through high-throughput SNPs genotyping analysis. All homozygous areas absent in unaffected subjects and shared among affected individuals will be identified using the Illumina GenomeStudio software. Good candidate genes which emerge will be sequenced in a conventional manner. The second half of the Ph.D. studentship will study the functional impact of these mutations on the immune system, using in vitro models including transfection of cells in tissue culture. It is likely that the student will focus on one of the two families studied in the first half of the project, although if time permits it may be possible to perform functional studies in both families dependent on the findings.

This exciting Ph.D. studentship will provide training in gene discovery using state of the art genetic mapping techniques, and next-generation sequencing; in addition the student will develop a portfolio of generic scientific and laboratory skills to study the functional implications of novel genetic variants discovered. This unique opportunity is made possible by the recent rapid developments in genetic technology, which now can be applied to a unique clinical cohort of patients with autoinflammatory disease looked after at GOSH. The student will join a vibrant and growing research group working in this area, and will be well supported by two post-doctoral research assistants working in this area, and by the primary and secondary supervisors. In addition, access to UCL genomics and bioinformatics expertise will be provided.

References:

1. French FMF Consortium (1997) A candidate gene for familial Mediterranean fever. *Nature Genetics* 17:25-31.
2. McDermott MF, et al. (1999) Germline Mutations in the Extracellular Domains of the 55 kDa TNF Receptor, TNFR1, Define a Family of Dominantly Inherited Autoinflammatory Syndromes. *Cell* 97:133-144.
3. Kastner DL, Aksentijevich I, Goldbach-Mansky R (2010) Autoinflammatory disease reloaded: a clinical perspective. *Cell* 140:784-790
4. Hoffman HM, et al. (2001) Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. *Nat Genet* 29:301-305.
5. Hawkins PN, et al (2003) Interleukin-1-receptor antagonist in the Muckle-Wells syndrome. *N Engl J Med* 348:2583-2584.
6. Liu Y et al (2012) Mutations in proteasome subunit beta type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. *Arthritis Rheum* 64:895-907.
7. Hawkins PN et al (2004) Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. *Arthritis Rheum* 50:607-612.
8. Hawkins PN, Bybee A, Aganna E, McDermott MF (2004) Response to anakinra in a de novo case of neonatal-onset multisystem inflammatory disease. *Arthritis Rheum* 50:2708-2709.
9. Hoffman HM (2009) Rilonacept for the treatment of cryopyrin-associated periodic syndromes (CAPS). *Expert Opin Biol Ther* 9:519-531.
10. Lachmann HJ et al (2009) Use of canakinumab in the cryopyrin-associated periodic syndrome. *N Engl J Med* 360:2416-2425.