How has the Study of Rare Diseases Influenced Our Knowledge of More Common Diseases?

When Harry Raymond Eastlack, Jr. (born 1933) died, his skeleton was almost completely fused into one continuous piece. Sheets of bone covered his back, while plates of bone locked his spine, jaw and skull. His limbs, shoulders, elbows, knees and hips were immobilised by ribbons of bone; his upper arms were fused to his breastbone by bridges of bone that crossed his immobilised rib cage[1]. Harry Eastlack suffered from a rare genetic disease few people would have heard of - fibrodysplasia ossificans progressiva (FOP), a disease also known as Stone Man syndrome. FOP progressively transforms the body's soft connective tissue into bone, causing patients who suffer from it to undergo a cruel, painful metamorphosis into permanent immobility and loss of physical freedom[2].

The European Union defines a rare disease as one that affects less than 5 in 10,000 of the population. There are about 6000 - 8000 known rare diseases to date, FOP being one of them. 80% of rare diseases have a genetic component and they are often chronic and life-threatening[3]. Across the globe, hundreds of millions of people are affected by a rare disease (6-8% of the population), and yet only a small number of these diseases have treatments. The need for research and recognition is so huge that rare diseases are often called "orphan diseases" because they are orphaned from society, from the medical profession, and from research. Whilst the ultimate aim of rare disease research is to discover their causes and to establish cures, studying rare diseases can also reveal key insights into common disease mechanisms, leading to an increased understanding of how they develop and how they might be treated or prevented. Many rare diseases are actually extreme forms of common diseases and share their characteristics[4, 5].

Research done on FOP has led to greater understanding of its more commonly occurring counterpart: non-hereditary heterotopic ossification (NHHO). Like FOP, NHHO is characterised by bone formation in soft tissues (usually muscular, adipose or connective), but is limited to the affected site and is not progressive. NHHO usually arises following trauma, certain arthropathies,

and particularly in the context of common age-related conditions such as common vascular pathology and after total hip arthroplasty for age-onset degenerative joint disease[7]. In FOP, tissue trauma leads to episodes of rapid new bone growth, and since NHHO often develops following injury and inflammation, it suggests that the formation of heterotopic bone in NHHO and ossification of soft tissues in FOP share similar initiating events. Whilst there are no cures for FOP to date, the discovery of the FOP gene (ACVR1/ALK2) in 2006 and emerging understanding of its mechanisms have led to some suggested strategies to the development of a treatment and prevention plans[7]. These strategies can also be applied to the treatment and prevention of NHHO. They are as follows[7]:

1. It was found that mutation of the FOP gene results in the formation of a mutant bone morphogenetic protein (BMP) receptor that sets off the series of events transforming various soft tissues into bone when triggered by tissue trauma. Development of a method of blocking the activity of this receptor would greatly reduce the incidence of heterotopic ossification.
2. Mouse models of heterotopic ossification strongly support an association between inflammation and heterotopic ossification. In one study, inflammatory pathways were activated in a constitutively active ACVR1/ALK2 mouse model and it led to heterotopic ossification at the inflammation sites; activation of the mutant ACVR1/ALK2 gene alone without inflammation did not trigger any heterotopic ossification. In another study, both pharmacological and genetic inhibition of circulating monocytes and macrophages led to significant reduction in heterotopic ossification. Thus, the blocking of inflammatory triggers can be a viable method of preventing FOP flare-ups and NHHO, particularly in the elderly with arthropathies and other age-related conditions that potentially lead to increased incidence of inflammation.
3. It was also recently found that the generation of a hypoxic microenvironment promoted heterotopic ossification. It has also been demonstrated that BMP signaling was prolonged

and amplified in the presence of mutant ACVR1/ALK2 under hypoxic conditions. Hence, the blocking of physiological responses to hypoxia can also be a possible method of inhibiting heterotopic ossification.

4. Finally, a study by Shimono et al. (2011) demonstrated that the activation of retinoic acid receptor gamma (RARγ) using retinoid agonists inhibited pre-cartilage and cartilage cells that follow from the inflammatory start signals. These are precursor cells that form the scaffolding for the synthesis of mature heterotopic bone. Importantly, when the RARγ agonists are removed, there is no significant rebound effect, suggesting that the RARγ agonist effect may be irreversible. The authors also successfully showed that retinoids are effective in inhibiting heterotopic ossification in animal models during the pre-cartilage mesenchymal stem cell phase, up to, but not including, the bone formation phase. They also found that retinoids are able to redirect mesenchymal stem cells to a non-bone lineage. This observation does not only have important implications for FOP and NHHO, but also for skeleton oncology, vascular biology, and tissue engineering!

Hence, it can be seen that the insights gained from FOP research have also led to new possibilities for cures and management/prevention strategies for more commonly occurring, non-FOP heterotopic ossification. Additionally, research done on FOP yielded spillover benefits in other areas of medical knowledge as described above.

Another example of rare disease research facilitating understanding of common diseases can be seen in the development of statins, which was largely aided by research done on familial hypercholesterolemia (FH). FH is a rare disorder in which the genes for the low-density lipoprotein (LDL) receptor are mutated, leading to very high plasma LDL concentrations and subsequent premature coronary artery disease, as well as aortic valve and root disease. The statins are a class of drugs that inhibit the co-enzyme HMG-CoA reductase, the rate-limiting enzyme in cholesterol

biosynthesis, thus lowering plasma LDL concentrations[8]. A landmark study by Goldstein and Brown in 1973 showed that cultured skin fibroblasts from subjects with FH displayed abnormally enhanced activity of HMG-CoA reductase, and it was found that the enhanced enzyme activity was the result of the absence of normal feedback suppression by LDLs, leading to the overproduction of cholesterol by the mutated cells[9]. The authors went on to discover cell-surface LDL receptors, which binds LDLs and regulates the rate at which cholesterol is transferred into the cell. Cells obtain cholesterol by increasing the number of LDL receptors on their surface and prevent over accumulation of cholesterol by suppressing the synthesis of these same receptors. Thus, it was established that defective LDL receptors led to failure in feedback mechanisms and increased cholesterol levels, and inhibiting HMG-CoA reductase was a viable solution to the problem[10]. Apart from directly lowering cholesterol production, inhibition of HMG-CoA reductase also leads to increased production of LDL receptors in liver cells, which allows increased cholesterol uptake and removal from the bloodstream[11]. Their groundbreaking research laid the foundation for the discovery of the first statin – mevastatin – by Japanese scientists Akira Endo and Masao Kuroda. They first isolated the compound from the mold *Penicillium citrinum* and found it to be a potent inhibitor of HMG-CoA reductase. Mevastatin was proven to significantly lower LDL levels in humans, leading to a decreased risk of atherosclerosis and coronary heart disease. The discovery of mevastatin was soon followed by the development of various statin analogues, such as lovastatin and simvastatin, and these have all been established as effective and safe cholesterol-reducing drugs, used by many patients globally[12].

FOP and FH research are just two examples of rare disease research that helped advance knowledge of more common diseases. Many more examples abound such as the use of the rare genetic disease alkaptonuria as a model to study osteoarthritis, the discovery of new obesity genes from the study of congenital leptin deficiency (a rare disease marked by severe early-onset obesity and over-eating), and increased understanding of uric acid metabolism and gouty arthritis from the

study of Lesch-Nyhan disease, a rare disease that causes uric acid overproduction and neurological dysfunction[5]. The key takeaway message is this: there is a great need to increase awareness and understanding of rare diseases, their impact, and their scientific importance. There is also a need for societies around the world to fully appreciate the fact that what is learned about rare diseases can have profound consequences for the understanding and treatment of more prevalent diseases. Wider international awareness of rare diseases can lead to greater investment and acceleration of research, and also help bring the patient community closer together, allowing for greater support networks to be formed. Global awareness of rare diseases is critical precisely because of their rarity and we need to approach the study of them on a global basis in order to be successful in discovering treatments and in improving the quality of life for patients. Such advancements in the knowledge of rare diseases will undoubtedly bring forth a harvest of new insights and discoveries of potential treatments for diseases from which millions more suffer[13].

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