42 Hereditary pancreatitis – managing patient clinical information and sequence variants in the *CFTR*, *PRSS1* and *SPINK1* genes

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Hereditary pancreatitis is an autosomal dominant disease with variable expression caused by mutations in the *PRSS1* gene. Two other genes, *SPINK1* and *CFTR* are risk factors for pancreatitis and can be inherited in an autosomal recessive or multifactorial fashion. Gene sequencing of all three genes aids in the diagnosis of hereditary pancreatitis which can be difficult to distinguish from a mild cystic fibrosis phenotype. Manageability of data derived from the patient's clinical presentation and sequencing results is vital to understand genotype/phenotype correlation, to help classify variants and to assure quality in laboratory reporting. To this end, we have employed the clinical data management software, Progeny, to track genotypic and phenotypic information on individuals and pedigrees. The database was customized for pancreatitis patients. Data entered included patient demographics and clinical presentation, laboratory sequencing results (nucleotide and amino acid changes for *CFTR*, *PRSS1* and *SPINK1*; mutation type and effect; and significance of the variant) and evidence for re-classification of variants. Analysis of 59 pancreatitis cases (classified as idiopathic, acute or chronic) found 10.2% of the patients carried one *CFTR* mutation, 6.8% carried one *CFTR* and one *SPINK1* mutation, 5.1% carried one *SPINK1* mutation, 5.1% carried one *PRSS1* mutation and 1.7% carried two *CFTR* mutations. No mutations were found in 71.2% of the cases. Progeny software allows customized databases for combining clinical and laboratory information, providing a means for accessible collection and querying of data.

43 Identification of novel mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in the Greek population

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Cystic Fibrosis has 5% carrier rate in the Greek population and one of the highest rates of mutation heterogeneity.

In this study we report 31 novel variants in the CFTR gene identified by DGGE analysis and direct sequencing. Of these 2 were frameshift mutations leading to premature termination codon, 20 missense, 5 synonymous variants and 4 intronic substitutions. The effects of these mutations were assessed in combination with the clinical phenotype and using *in silico* analysis. The missense mutations were assessed using "*PolyPhen*", "*SIFT*" and "*Pmut*". The impact of the silent mutations and the intronic substitutions on splicing elements was analysed using "*SSF*: Splicing Sequences Finder". Majority of findings included changes in splicing factor binding (not all data presented in the Table).

These new findings pose difficulty in counselling, especially when they involve couples where one member carries an established mutation and the other a novel variant. The only way to verify the true effect of these variants is to perform functional studies (of the missense mutations) and RNA studies (of synonymous variants and intronic substitutions) to confirm the effect on splicing.

Exon	Mutation	Phenotype	Polyphen result	SIFT result	Pmut result
4	c.538insACfs153X	Classic CF	N/A	N/A	N/A
20	c.3946delTGfs1300X	Classic CF	N/A	N/A	N/A
11	p.L541P	Azoospermia	Probably damaging	Not tolerated (0.00)	Pathological (6)
15	p.P936T	Atypical CF	Probably damaging	tolerated (0.38)	Pathological (4)
10	p.S945Y	General population screening	Probably damaging	Not tolerated (0.00)	Pathological (2)
1	p.M1R	Asthma	Probably damaging	Not tolerated (0.00)	Pathological (7)
11	p.M595V	General population screening	Probably damaging	Not tolerated (0.02)	Neutral (2)
19	p.K1165T	Bronchitis	Possibly damaging	Not tolerated (0.04)	Pathological (6)
15	p.S977C	General population screening	Possibly damaging	Not tolerated (0.01)	Pathological (5)

44 An adherence study using data from an AAD device in cystic fibrosis comparing early and late diagnoses

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Background: In our District General Hospital (DGH) the CF multidisciplinary team made a generalised observation that a group of patients diagnosed with CF late (5–9 yrs old) had very poor adherence. We decided to do a small study to objectively identify if this was the case and what other significant barriers to adherence exist.
Objectives: To systematically identify the barriers to treatment adherence for children with CF in a DGH. To examine any relationship between these barriers, primarily whether or not a late or early diagnosis has any effect on adherence with CF.
Methods: A quantitative design with adherence data was electronically monitored via an AAD device. We used the Overall usage of the device as a percentage (over the same 3 month period) for administering Promixin. 8/17 children with CF were selected in accordance with the inclusion criteria, and put into 2 groups; 4 with early diagnosis (<1 year) 4 with late diagnosis (>5 years). Age now 9–18 years.
Results: The early diagnosis group had improved adherence (Mean 61.33% SD), than the later diagnosed group (Mean 27%) with the AAD device. This was highly significant ($p \leqslant 0.016$), according to the t-test. Adherence was not associated with any other variables apart from age at diagnosis.
Conclusion: Overall, adherence with an AAD device was significantly improved for those children who were diagnosed within the first year of life than those with a later diagnosis. Barriers to adherence need to be identified to enable the CF team and families to act upon them and avoid important health consequences. Can we assume that this poor adherence extends to other important aspects of their CF care? Physiotherapy for example?

45 Validation of ISEsweat: a new device for the direct measurement of sweat chloride concentration (SCC) for the diagnosis of cystic fibrosis

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Introduction: The SCC remains the gold standard for the diagnosis of Cystic Fibrosis (CF). In newborn babies the amount of sweat collected to measure chloride concentration may not be enough and delay the diagnosis. We designed a new analyzer device for direct measurement of SCC (ISEsweat).
Aims: To assess both the performance and safety of the ISEsweat was compared with the gold standard quantitative pilocarpine iontophoresis test (Q.P.I.T.).
Methods: The ISEsweat uses disposable sensors for the direct quantitative determination of SCC. Three CF Units participated. At each one, trained staff performed both methods simultaneously. For the statistical analysis, the Bland–Altman and the intraclass correlation coefficient (ICC) were used to compare two methods.
Results: 42 individuals aged between 7 and 57 years participated in the study. 18 with CF and 24 healthy volunteers as controls. In CF patients SCC with the ISEsweat device was 106.8±13.81 mmol/L compared to 111.7±17.58 mmol/L with the standard SCC.In healthy volunteers with the ISEsweat device was 19.2±9.48 mmol/L compared to 26.4±11.79 mmol/L with the standard SCC. There as a good correlation, between both methods using ICC = 0.95 was found ($\alpha = 0.05$) No adverse effects detected during this clinical assay.
Conclusions: We concluded that ISEsweat is a valid and safety new device for SCC measurement. These preliminary results are very encouraging and warrant further research with larger samples of patients, to confirm that the ISEsweat can become a useful tool for the diagnosis of CF and even prove to be a reliable more convenient alternative method to the reference sweat test as approved by current guidelines.