

Copy Number Variants (CNVs) Affecting Cancer Predisposing Genes (CPGs) Detected As Incidental Findings In Routine Germline Diagnostic Chromosomal Micro-Array (CMA) Testing

Josie Innes¹, Lisa Reali², Jill Clayton-Smith¹, Georgina Hall¹, Derek Lim², George Burghel¹, Kim French¹, Unzela Khan¹, Daniel Walker¹, Fiona Lalloo¹, D. Gareth R. Evans¹, Dom McMullan², Eamonn R. Maher³, and Emma R. Woodward²

1. Manchester Centre for Genomic Medicine, St Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, M13 9WL, UK.

2. West Midlands Regional Genetics Service, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, B15 2TG, UK

3. Department of Medical Genetics, University of Cambridge and NIHR Cambridge Biomedical Research Centre and Cancer Research UK Cambridge Centre, CB2 0QQ, UK.

Corresponding author:

Dr Emma R. Woodward

Manchester Centre for Genomic Medicine, St Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, M13 9WL, UK

Emma.Woodward@cmft.nhs.uk

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Abstract

Background

Identification of copy number variations (CNVs) through chromosomal microarray (CMA) testing is first line investigation in individuals with learning difficulties/congenital abnormalities. Although recognised that CMA testing may identify CNVs encompassing a cancer predisposition gene (CPG), limited information is available on the frequency and nature of such results.

Methods

We investigated CNV gains and losses affecting 39 CPGs in 3,366 pilot index case individuals undergoing CMA testing, and then studied an extended cohort (n=10,454) for CNV losses at 105 CPGs and CNV gains at 9 proto-oncogenes implicated in inherited cancer susceptibility.

Results

In the pilot cohort, 31/3,366 (0.92%) individuals had a CNV involving one or more of 16/39 CPGs. 30/31 CNVs involved a tumour suppressor gene (TSG), and 1/30 a proto-oncogene (gain of *MET*). *BMPRI1A*, *TSC2* and *TMEM127* were affected in multiple cases. In the second stage analysis, 49/10,454 (0.47%) individuals in the extended cohort had 50 CNVs involving 24/105 CPGs. 43/50 CNVs involved a TSG and 7/50 a proto-oncogene (4 gains, 3 deletions). The most frequently involved genes, *FLCN* (n=10) and *SDHA* (n=7), map to the Smith-Magenis and cri-du-chat regions respectively.

Conclusion

Incidental identification of a CNV involving a CPG is not rare and poses challenges for future cancer risk estimation. Prospective data collection from CPG-CNV cohorts ascertained incidentally and through syndromic presentations is required to determine the risks posed by specific CNVs. In particular, ascertainment and investigation of adults with CPG-CNVs and adults with learning disability and cancer, could provide important information to guide clinical management and surveillance.

Introduction

The human genome contains marked structural variation and it is over 10 years since the first comprehensive copy number variant (CNV) map of the human genome was published (1). For children presenting with developmental delay/learning difficulties and/or congenital abnormalities, diagnostic germline chromosomal microarray (CMA) for causative CNVs is now a first line investigation and, together with advances in CMA technology leading to improving resolution (2), there are increasingly numbers of patients identified with CNVs of uncertain significance or for which the resulting phenotype is unclear. This is particularly pertinent where an identified CNV encompasses an inherited cancer (cancer predisposition gene/CPG) and there is no relevant personal or family history, a so-called incidental finding.

With the mainstreaming of modern genomic investigations, CMA testing is often ordered by non-genetics health care professionals (e.g. paediatricians) who may have limited familiarity with familial cancer syndromes and are unable to advise on the full significance of the CMA result. Previously, Pichert et al (3) described the frequency of CNVs affecting 47 CPGs in 4,805 CMA analyses. We report an independent replication study on a larger patient cohort (two fold increase in cases and a more extensive CPG list (n=105)).

Methods

Participants and samples

Samples were referred by paediatricians and clinical geneticists where constitutional diagnostic array comparative genomic hybridisation (aCGH) was requested to determine causes of developmental delay, learning difficulties, neurocognitive impairment and/or birth defects. Only arrays pertaining to the index case in a family were included. The following were excluded (i) patients with clinical features and/or a family history suggestive of the involvement of a known cancer predisposing gene (CPG) (ii) samples from prenatal diagnoses; and (iii) results involving whole chromosome or chromosome arm aneuploidy (iv) results where the CNV identified involving a CPG was present in mosaic form. Monozygotic twins were counted as one individual for the purposes of this study. A finding was considered positive where the involvement of a CPG was not suspected before testing (i.e. an incidental finding). CNVs included in the results were those where the CNV was considered to be causative of the index case' presenting features, and also CNVs of either benign or uncertain significance. Approval for the clinical audit study was provided by Birmingham Women's NHS Foundation Trust and Central Manchester University Hospitals NHS Foundation Trust.

Two cohorts of patients were analysed in two stages. Initially, a pilot cohort comprising 3,366 index case samples investigated between 1 Jan 2009 – 30 Sept 2013 at the West Midlands Regional Genetics Laboratory and then an extended cohort comprising 10,454 index case samples between 1 Jan 2011 and 31 Dec 2015 at the Manchester Centre for Genomic Medicine.

Gene Search Lists

The pilot cohort (n=3,366) was analysed for CNV gains and losses involving a core set of 39 genes (4 oncogenes, 35 tumour suppressor genes) associated with familial cancer predisposition syndromes (Table S1). In the 10k extended cohort (10,454 index patients), CNV losses were investigated in a panel of 105 known CPGs (including the 39 genes analysed in the pilot cohort) comprising, 94 genes on the Illumina Trusight Cancer Panel (4) and 11 further candidate CPGs [*CDKN1B*, *CDKN2B*, *ESR2*, *HIF2A*, *HOXB13*, *PDGFRA*, *POLD1*, *POLE*, *SMARCA4*, *SMARCE1*, *SDHA* (5-15)].

Additionally, in the 10k extended cohort, CNV gains at nine of the 105 genes [*ALK*, *EGFR*, *HRAS*, *RHBDF2*, *CDK4*, *KIT*, *MET*, *PDGFRA*, *RET* (10, 16-23)] were investigated as activating alterations have been described in hereditary cancer predisposition. Partial or whole gene losses and gains were noted and counted as positive findings.

Laboratory methods and bioinformatics analysis

Testing was undertaken in CPA accredited laboratories. aCGH analysis was carried out using DNA extracted from peripheral blood or mouthwash samples using standard techniques.

For the pilot cohort, aCGH was carried out using either the BlueGnome CytoChip 1Mb BAC (Bacterial Artificial Chromosome) array or the BlueGnome 8x60k v2.0 (ISCA) design oligonucleotide array. aCGH data analysis was performed using BlueFuse Multi software. Copy number variant (CNV) detection using the BlueGnome 1Mb BAC array was carried out with a successful BAC inclusion threshold of >95%. Single clones were called as copy number variants using Log₂ thresholds of +/-0.3. Copy number variant (CNV) detection using the BlueGnome 8x60k v2.0 (ISCA) design oligonucleotide array was carried out with a minimum 3 probe inclusion using Log₂ ratio thresholds of +/-0.3. No minimum size threshold was applied for either platform.

For the 10k extended cohort, aCGH testing was carried out using Oxford Gene Technology (OGT) CytoSure™ ISCA v2 (8x60k) arrays for all cases with the exception of P102 which was tested using OGT CytoSure™ Constitutional v3 Array (8x60k). aCGH data analysis was performed using OGT CytoSure™ Interpret software. Copy number variant (CNV) detection was based on a minimum 4 probe inclusion using Log₂ thresholds of ≥ 0.35 for gains and ≤ -0.6 for losses, and no minimum size threshold applied.

For both studies, automatically called CNVs were subject to manual assessment to exclude artefacts and a manual screen for mosaic aberrations was also performed. Inheritance studies were performed using karyotype analysis, targeted aCGH or *in situ* hybridisation studies, as appropriate where parental samples were available.

CNV co-ordinates described are based on the minimum affected region as per standard practice and all co-ordinates are GRCh37/hg19 except where otherwise stated.

Statistical Analysis

Data are displayed as mean \pm SD. Continuous data were analysed using a two-tailed Student's t-test. A *P*-value < 0.05 was considered to be statistically significant.

Results

Stage 1: Pilot Cohort Analysis

Within the 3,366 index patients there were 31 individuals (15 males, 16 females) harbouring 31 CNVs involving one or more of the 39 CPGs analysed (Table S2). The ‘incidental finding’ rate was 0.92% (31/3366). Mean age at CNV analysis in individuals with a positive finding was 51.9 months (SEM 14.2, range 0-312 months, median 8 months). In 16/31 cases the CPG-related CNV was considered to be relevant to the clinical phenotype and in 15 individuals the CNV identified was considered to be either unrelated or of uncertain clinical significance. In 10 cases the CNV encompassing the cancer gene was *de novo* and in 14 cases the CNV was inherited (including one where the child inherited the unbalanced form of a parental balanced translocation). The family history was known in 11 of the 14 cases where the CNV was inherited (excluding the case with the unbalanced form of the parental translocation), and there were no clinical features in keeping with a germline pathogenic alteration of the CPG.

Only one of the CNVs involved an oncogene, a gain encompassing *MET*. The remaining 30 CNVs (20 gains and 10 losses) involved a tumour suppressor gene and two CNVs affected multiple CPGs: a gain involving *MSH2* and *MSH6*; and a deletion encompassing *BMPRIA* and *PTEN* thought likely causative of the learning difficulties phenotype. In six cases the CNV arose as consequence of a complex chromosomal rearrangement and, in all six, resulted in the gain of a tumour suppressor gene (*TSC2* x3, *PMS2* x1, *VHL* x2). The 31 “incidental findings” CNVs involved 16/39 (41.0%) CPGs in the pilot stage gene list with *BMPRIA* (in 6 cases), *TSC2* (n=4) and *TMEM127* (n=3) affected in multiple cases (Fig. 1).

Stage 2: Extended Cohort Analysis

49 (17 females, 32 males) of 10,454 individuals (0.47%) had a total of 50 CNVs involving one or more CPGs on the Stage 2 gene list (see Table S1 and Table S3). The mean age at aCGH in individuals with a positive finding was 87.5 months (SEM 15.0, range 0-460 months, median 46.5 months). In 40 of the individuals the array finding involving the cancer gene was thought to be causative of the clinical phenotype in the index individual and in 9 cases the CNV identified was of uncertain clinical significance or unrelated to the *presenting* features. In 27 cases the CNV arose *de novo* and in 6 cases the CNV was inherited. In 3 of

these 6 cases the child had inherited the unbalanced form of a parental balanced translocation. In the remaining 3 cases, the family history was known in 2 cases and there were no clinical features in keeping with a germline pathogenic alteration of the CPG.

7 of the 50 CNVs involved an oncogene: 4 gains (*HRAS* x2, *MET* and *PDGFRA*) and 3 deletions (*MET*x2, one involving both *KIT/PDGFRA*). The remaining 43 CNVs were deletions involving TSGs. In one case there was a heterozygous contiguous deletion of two TSGs (*BLM* and *FANCI*). Four of the CNVs (in three individuals) arose as a consequence of complex chromosomal rearrangement resulting in gain of an oncogene in three cases (*HRAS* x2, *MET* x1) and loss of a tumour suppressor gene (*SDHA*) in one. These 50 CNVs affected 24 of the 105 genes on the search list ($24/105 = 22.9\%$) with CNVs affecting *FLCN* accounting for 10/50 (20%) and of *SDHA* 7/50 (14%) (Fig. 2).

Joint Analysis of Stage 1 and Stage 2 data sets and CPG lists

Oncogene gains: 3 of 13,820 cases (0.02%) in the combined Stage 1 and Stage 2 cohorts had a CNV gain at one or more of the 4 oncogenes (*RET*, *PDGFRA*, *MET* and *KIT*) in the Stage 1 gene list with CNV gains occurring twice at the *MET* locus (including one individual with a complex rearrangement leading to gain) and once at the *PDGFRA* locus. Three individuals had a deletion of one or more of these oncogenes (including the one individual with the deletion of both *MET* and *PDGFRA* and two with a deletion of *MET*) (Table S4).

TSG losses: 30 of 13,820 (0.22%) individuals in the combined Stage 1 and 2 cohorts had a partial or whole deletion involving one or more of 35 tumour suppressor genes (Table S4). In 22/30 cases the CNV identified was thought to be causative of the child's presenting features and was thought to be either unrelated to, or of uncertain significance, in the remaining eight. In 17 cases the CNV identified was *de novo* and was found to be inherited in 6 individuals (including one where the child had inherited the unbalanced form of the parental balanced translocation). 15 of the 39 (38.5%) genes on the common search list (12 tumour suppressor genes and 3 oncogenes) were affected by a deletion CNV with *SDHA* being involved in 9 CNVs and *BMPRIA* in 6 (Fig. 3) (Table S4).

CNVs encompassing CPGs residing within the known chromosomal microdeletion regions: 17p11.2 and 5p15.22

10 individuals (Stage 2 cohort) had a CNV encompassing *FLCN* (chr17:17,115,527-17,140,502) which resides within the Smith-Magenis Syndrome (SMS) region on 17p11.2 (Decipher chr17: 16,773,072 – 20,222,149) (24), accounting for 20% of the total CNVs identified (Fig. 2, Fig. 4). Five of the CNVs were known to be *de novo* and in five the inheritance was unknown. In four individuals (P113, P111, P116, P119) the majority of the CNV overlapped with but did not encompass the SMS region. In the remaining six, the SMS region was contained within the CNV.

Nine individuals (two from Stage 1 and seven from Stage 2) had a deletion encompassing *SDHA* (chr5:218,356-256,814) which resides toward the 5' end of the cri-du-chat Region (Decipher chr5:10,001 – 12,533,304) (24) accounting for 26.0% of the total number of CNVs identified in the combined cohorts (Fig. 3, Fig. 5). In five individuals the CNV was within the cri-du-chat region and, in the remaining four, the CNV identified extended 3' beyond the critical region (Fig. 5). The CNV was inherited in three individuals (including the individual with the unbalanced translocation leading to loss of *SDHA* and gain of *HRAS*), *de novo* in two and inheritance was unknown in four individuals.

Discussion

CMA testing is now routinely ordered for individuals presenting with undiagnosed learning difficulties and/or developmental abnormalities and is often undertaken outwith the genetics clinic, for example in the paediatric mainstream setting.

Whilst these investigations provide the opportunity for diagnosis, the CNVs identified may encompass or involve genes where intragenic alteration or whole gene copy number losses are known to be associated with predisposition to other condition(s) unrelated to the presenting features and can be classed as incidental findings. Unlike other genome wide molecular genetic diagnostic strategies, such as whole exome and genome sequencing for which results can be filtered in a gene specific manner, identified CNVs are usually visible to the investigator. Incidental finding CNVs involving CPGs can present significant counselling challenges as (i) whilst the phenotype and cancer risks of intragenic mutations in a CPG may be well defined the risks associated with large CNVs are often unclear as deletion of additional *in cis* genes might modify cancer risks (25); (ii) the known cancer risks associated with CPGs are for individuals ascertained because of a family history and are likely to be lower for population-based ascertainment; and (iii) most CNVs involved CPGs associated with later onset cancers whereas CMA is more commonly performed in a paediatric setting (mean age at positive finding in our pilot and extended cohorts was 51.9m and 87.5m respectively). Nevertheless CPG-CNVs cannot be ignored - as exemplified by two infants (P136 and P137, ages at aCGH 0m and 3m respectively) with deletions of ~50Mb and 24.5Mb respectively encompassing *RBI* who subsequently developed clinical retinoblastoma after the CMA was requested. Whilst retinoblastoma is highly penetrant at a young age (mean age diagnosis of bilateral retinoblastoma 15m) (26), and the tumour penetrance for intragenic mutation of other CPGs is often more variable, this highlights that CNVs encompassing a CPG may be of clinical consequence and should be considered as a paradigm for the need to report such findings until more is known regarding their effects.

Indeed recent analysis of a range of CPGs showed that large deletions including whole gene deletions were associated with fairly typical cancer predisposition compared to point mutations (27). Deletions of CPGs with substantial childhood onset risks such as *SMARCB1* (malignant rhabdoid tumour) and *TP53* (brain and sarcoma) also appear to be not infrequent and there is no evidence these deletions are less penetrant than

point mutations (27). On the other hand, we also detected an inherited deletion encompassing *BMPRIA* (P005) where there was no family history of polyposis. Whilst *BMPRIA* mutations are of lower penetrance than *RBI* (28), it is likely that other factors influencing penetrance/expression are also involved. Varying phenotypic consequences of large deletions encompassing disease-causing genes are a recognised challenge (29) and the mechanisms underlying such variable phenotypic effects may include combinations of underlying genomic architecture, long range regulatory effects and, more recently recognised, the influence of topology associated domains (30). In addition, for CNVs involving TSGs the somatic “second hit” might result in homozygous loss of many genes in the cancer cell and result in non-viability through loss of an essential gene or by producing, in combination with loss of the CPG, a synthetic lethal state (31).

In four individuals we identified partial deletions of a TSG. Whilst with CMA it is not possible to precisely characterise the breakpoints, we would expect multi-exon deletions to be pathogenic, particularly where they have been described in the corresponding familial cancer syndrome (32-35). However, in these partial deletion cases we cannot exclude the possibility of expression of an abnormally truncated gene product, although one patient, (P029), did subsequently develop features of tuberous sclerosis indicating pathogenicity.

For CNVs resulting in the gain of a TSG or proto-oncogene, the phenotypic consequences can also be very difficult to interpret. CMA gives no positional information (other than where there is also a cytogenetically characterised complex rearrangement, as occurred in 8 individuals) and a CMA-detected copy number gain might be caused by an intragenic duplication that inactivated a TSG or gain of a functional proto-oncogene – either of which might be associated with a cancer risk.

The CPGs most commonly involved in CNVs were *SDHA* and *FLCN* and both reside within the chromosomal micro-deletion regions for cri-du-chat (Decipher chr5:10,001–12,533,304) and Smith-Magenis (Decipher chr17: 16,773,072 – 20,222,149) respectively (24, 36-37). Although toward the 5' end, *SDHA* is within the cri-du-chat deleted region which has an incidence of 1:15,000 – 1:50,000 (38). Intragenic *SDHA* inactivating mutations may be associated with pheochromocytoma, paraganglioma and gastrointestinal stromal tumours (GIST) (15, 39). Though the penetrance of familial *SDHA* mutations has been estimated at ~40% by age 40 years (40), other evidence suggests that the penetrance is much lower (39) and to date we

are not aware of any *SDHA*-related tumours reported in patients with cri-du-chat (41). Nevertheless, subject to appropriate ethical considerations, it would be of interest to investigate adults with cri-du-chat deletions involving *SDHA* for subclinical evidence of *SDHA*-related tumours.

FLCN lies within the Smith-Magenis syndrome (SMS) region, on 17p11.2 and accounted for 20% of the CNVs identified. Germline mutations in *FLCN* cause Birt-Hogg-Dube (BHD) syndrome which is characterised by the appearance of fibrofolliculomas from the third decade and renal cell carcinoma in about 25-30% of cases (42). RCC has been described in patients with SMS (43) but the precise risk of RCC in SMS patients with *FLCN* loss is unclear and further information is required to determine whether surveillance for RCC should be offered routinely. Nevertheless, in the presence of lung cysts or fibrofolliculomas (which on average precede RCC in BHD syndrome) it would seem prudent to do so.

Our CNV detection rate encompassing a CPG was between 0.3% (Stage 1 and 2 combined, n=13,820) and 1% (Stage 1 pilot, n=3,366) in individuals undergoing diagnostic CMA. Pichert et al (2011) found CNVs affecting CPGs in 0.6% of 4805 diagnostic arrays and Boone et al (44) detected 0.9% in 9,005 arrays although this study involved a search list of 40 genes involved in adult onset disorders not specifically focussed toward cancer genes.

This study is the largest to date of CNVs affecting CPGs detected as incidental findings has demonstrated that optimal management of incidentally detected CPG-CNVs and will require systematic collection of long-term follow up data and international data sharing. In particular detailed studies of the clinical significance of *SDHA* and *FLCN* loss in patients with cri-du-chat and SMS would address the most frequently detected CPG-CNVs. Though CMAs are routinely performed in children with learning disability, significant numbers of adults with learning disability are likely not to have had high resolution CMA testing and routine reinvestigation of such patients could provide important information on cancer risks. In addition, we are compiling a database of adults with pathogenic CNVs and cancer and request that appropriate cases should be notified to Emma.Woodward@cmft.nhs.uk .

Contributorship Statement

Josie Innes undertook the data extraction and analysis and contributed to the writing of the manuscript. Lisa Reali undertook the data extraction and analysis and contributed to the writing of the manuscript. Jill Clayton-Smith contributed to the study design. Georgina Hall contributed to the data extraction. Derek Lim undertook data extraction and analysis and contributed to the writing of the manuscript. George Burghel undertook data analysis. Kim French undertook data extraction. Unzela Khan undertook data extraction. Daniel Walker undertook data extraction. Fiona Laloo contributed to the study design. D. Gareth R. Evans contributed to the writing of the manuscript. Dom McMullan contributed to the overall study design. Eamonn R. Maher contributed to the overall study design and writing of the manuscript. Emma R Woodward (ERW) was responsible for the overall design and content of the study and is overall guarantor for the study. ERW also wrote the manuscript.

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Competing Interests

There are no conflicts of interest to declare.

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Figure Legends

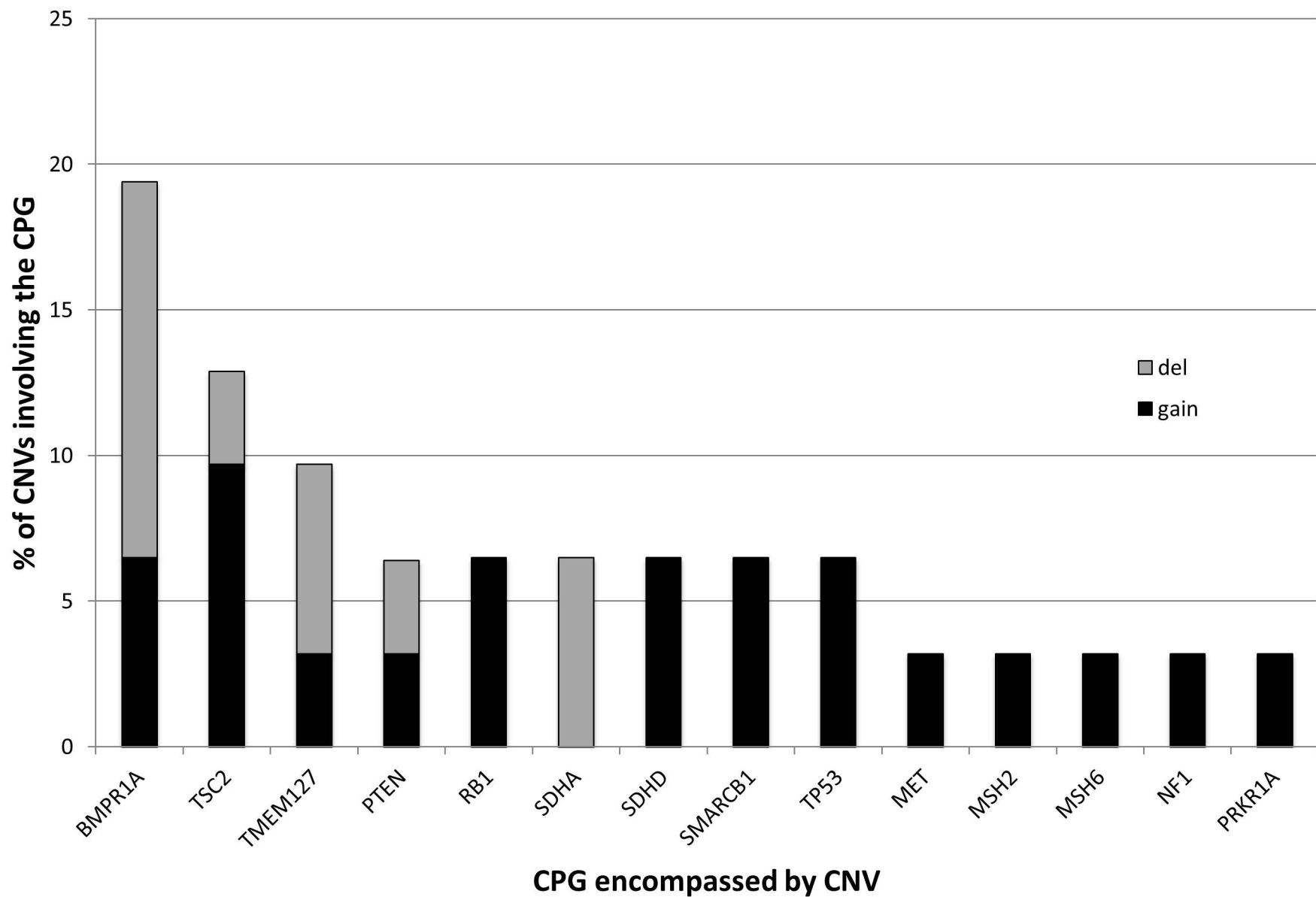
Figure 1. Percentage of CNVs detected in the Stage 1 pilot cohort affecting the CPG shown and whether the CNVs detected were gains or deletions. Where a CPG gene present in Table S1 is not shown then no CNV involving it was detected.

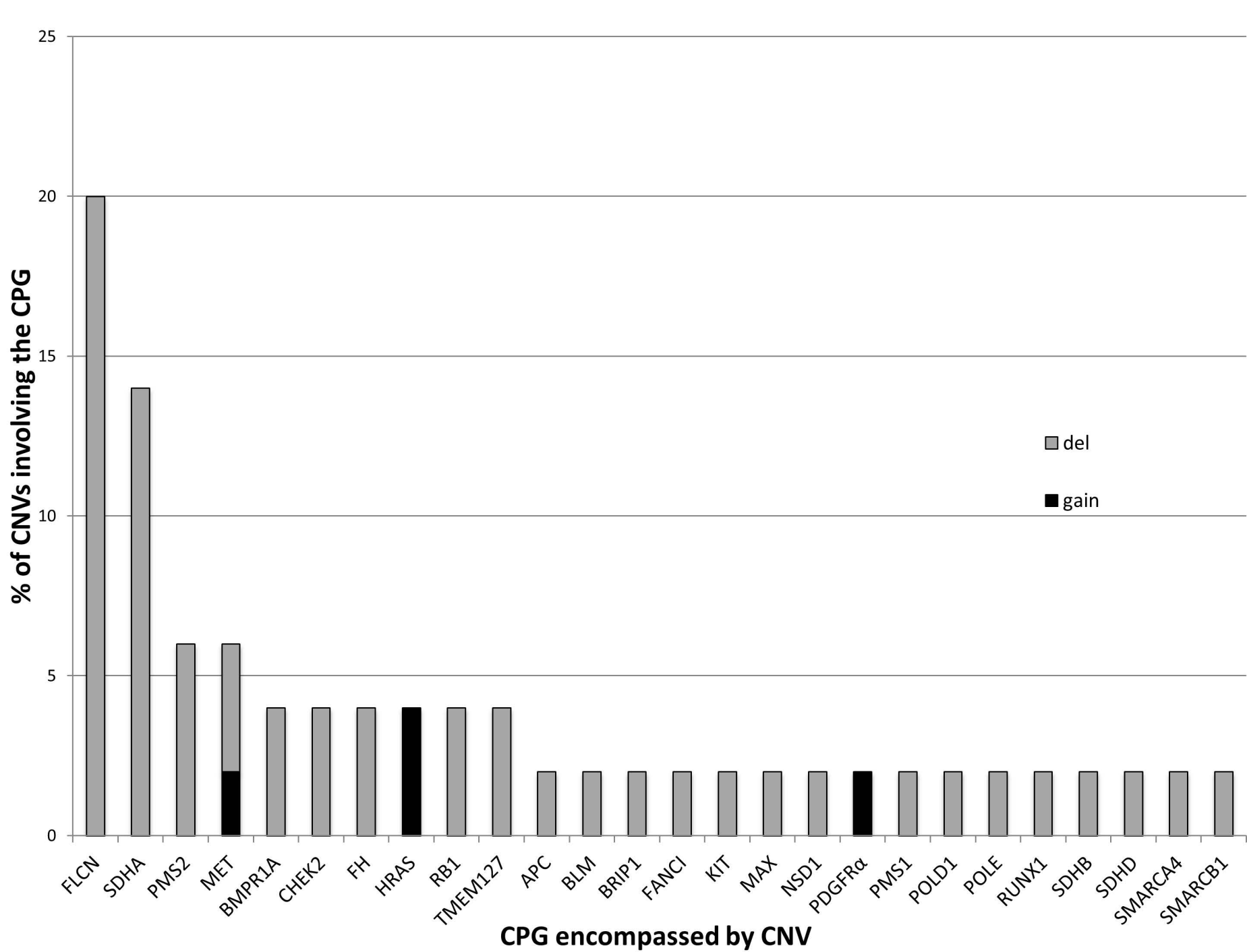
Figure 2. Percentage of CNVs detected in the Stage 2 extended cohort affecting the CPGs shown and whether the CNVs detected were gains or deletions. Where a CPG is not shown then no CNV affecting it was detected.

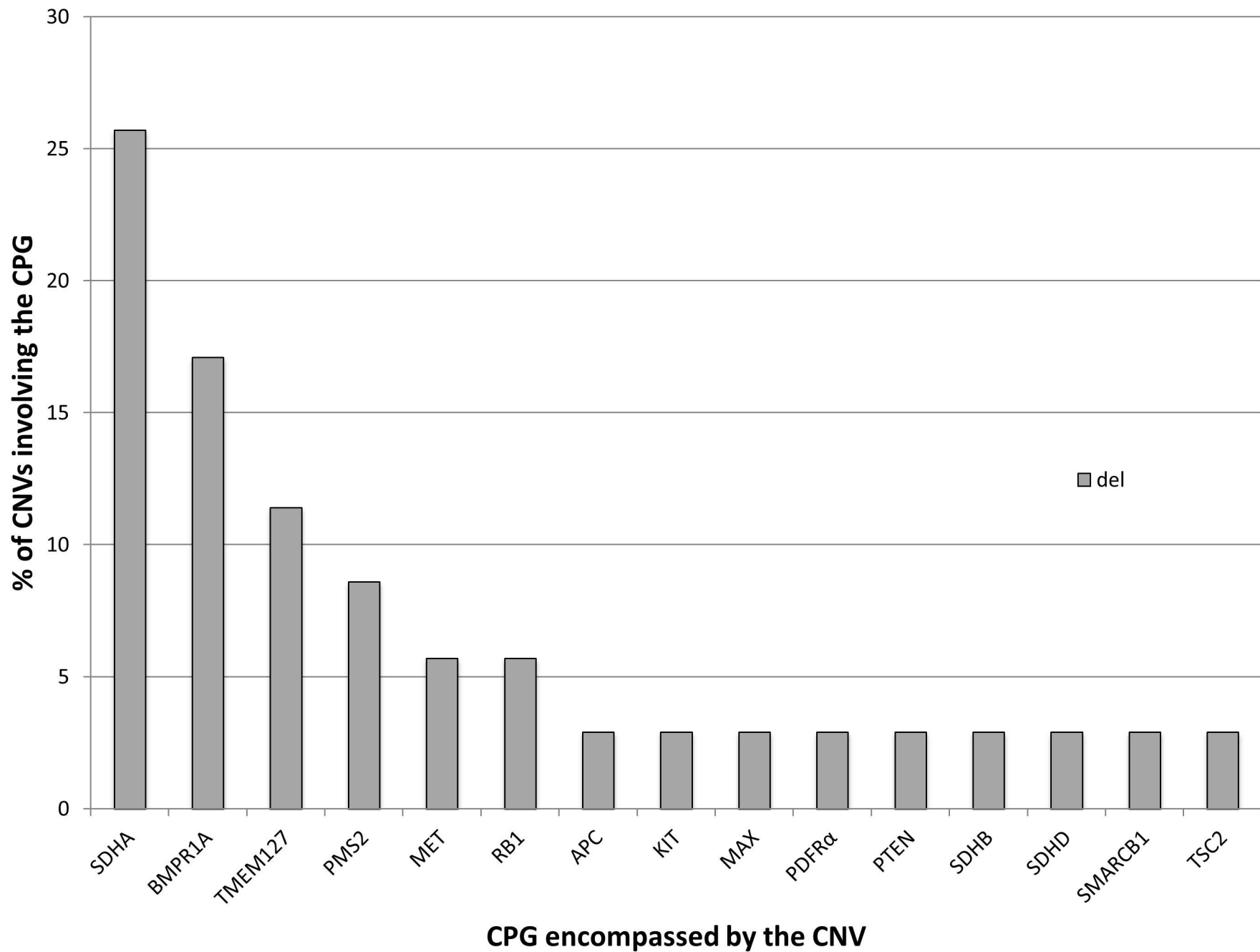
Figure 3. Percentage of deletion CNVs detected in the combined Stage 1 pilot and Stage 2 extended cohorts affecting the CPGs shown. Where a CPG is not shown then no deletion CNV affecting it was detected.

Figure 4. Schematic diagram of the 10 CNVs encompassing *FLCN* relative to the mid-point of *FLCN*. Each bar represents the CNV identified in the patient shown. The central axis represents the mid-point of *FLCN*, and the distance in base-pairs from this mid-point is shown on the horizontal X-axis.

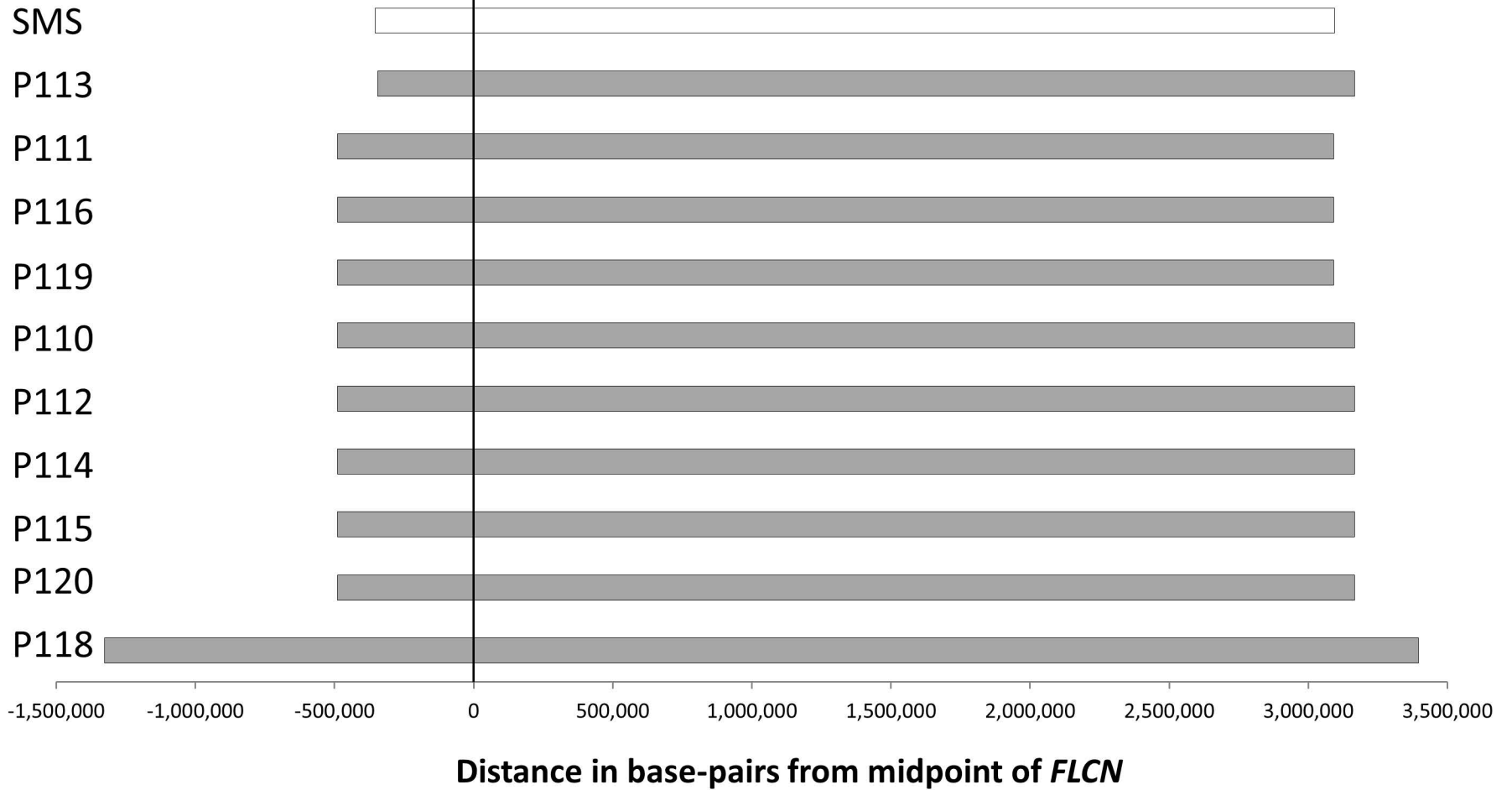
Figure 5. Schematic diagram of the 9 CNVs encompassing *SDHA* relative to the mid-point of *SDHA*. Each bar represents the CNV identified in the patient shown. The central axis represents the mid-point of *SDHA*, and the distance in base-pairs from this mid-point is shown on the horizontal X-axis.







midpoint of *FLCN*



midpoint of *SDHA*



Cri du chat

P139

P141

P140

P143

P144

P121

P015

P142

P016

-1,000,000 1,500,000 4,000,000 6,500,000 9,000,000 11,500,000 14,000,000 16,500,000 19,000,000 21,500,000 24,000,000

Distance in base-pairs from midpoint of *SDHA*

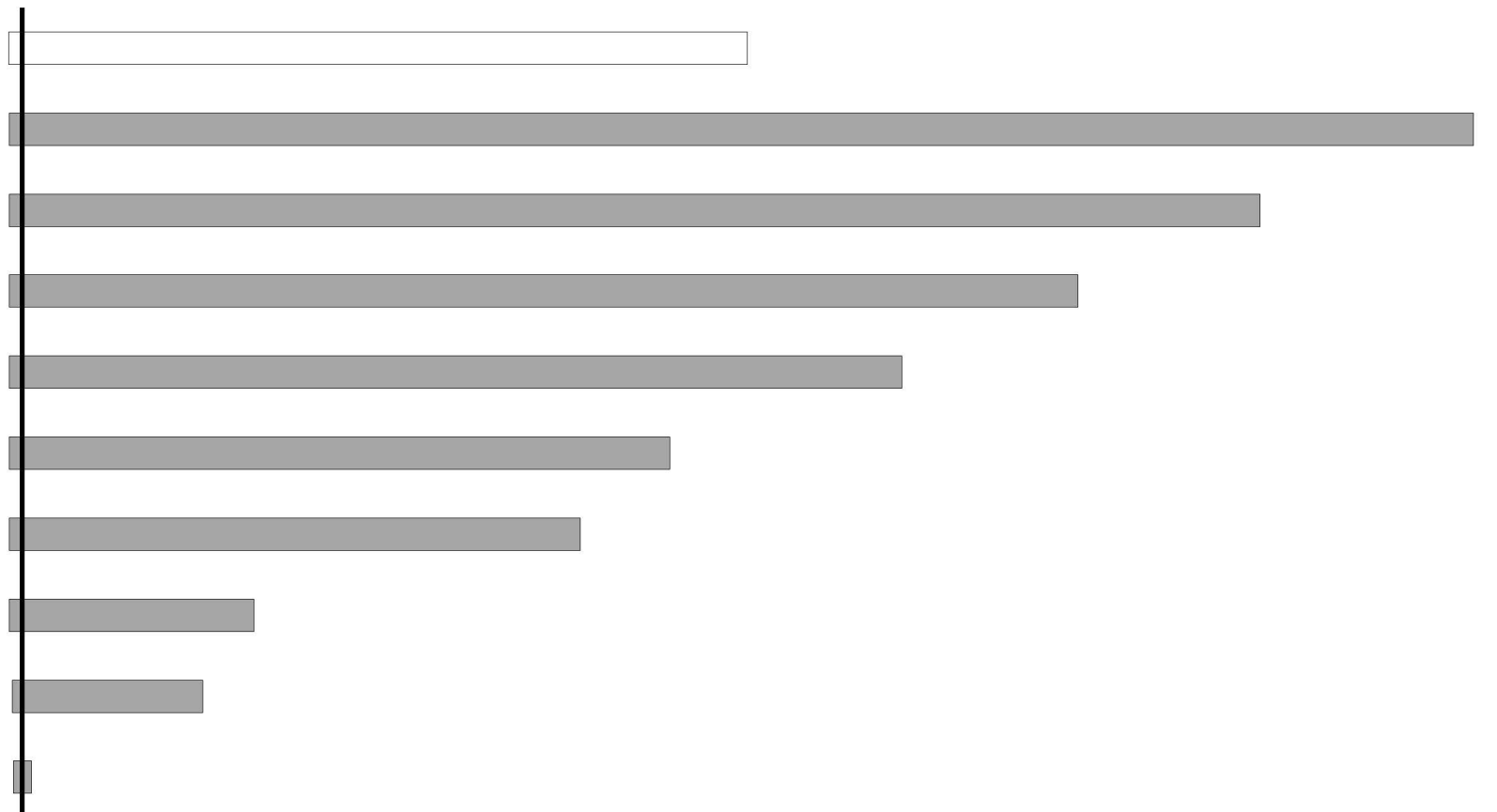


Table S1. Cancer Predisposing Genes (CPGs).

CPG	CPG in Pilot Cohort Analysis ?	CPG in Extended Cohort Analysis?	CPG MIM number	Chromosomal Location	Bi-allelic or Mono-allelic (with respect to cancer predisposition)	Condition associated with tumour predisposition	Phenotype(s) MIM number(s)
AIP	No	Yes	605555	11q13.3	Monoallelic	Pituitary adenoma predisposition	600634 / 102200
ALK*	No	Yes	105590	2p23.2-23.1	Monoallelic	Neuroblastoma susceptibility	613014
APC [#]	Yes	Yes	611731	5q21-q22	Monoallelic	Familial Adenomatous Polyposis Coli	175100
ATM	No	Yes	607585	11q22.3	Monoallelic	Breast cancer susceptibility	114480
					Biallelic	Ataxia Telangiectasia	208900
BAP1	No	Yes	603089	3p21.1	Monoallelic	Tumour Predisposition Syndrome	614327
BLM	No	Yes	604610	11q26.1	Biallelic	Bloom Syndrome	210900
					Monoallelic	Colorectal cancer susceptibility	114500
BMPR1A	Yes	Yes	174900	10q23.2	Monoallelic	Juvenile Polyposis Syndrome	174900
BRCA1	Yes	Yes	113705	17q21.31	Monoallelic	Breast and ovarian cancer susceptibility	PS604370
BRCA2	Yes	Yes	600185	13q13.1	Monoallelic	Breast and ovarian cancer susceptibility	PS604370
					Biallelic	Fanconi anaemia (D1)	605724
BRIP1	No	Yes	605882	17q23.2	Monoallelic	Breast cancer susceptibility	114480
					Biallelic	Fanconi anaemia (J)	609054

BUB1B	No	Yes	602860	15q15.1	Biallelic	Mosaic Variegated Aneuploidy Syndrome 1	257300
CDC73	Yes	Yes	607393	1q31.2	Monoallelic	Hyperparathyroidism-jaw tumour syndrome	145001
CDH1	Yes	Yes	192090	16q22.1	Monoallelic	Hereditary diffuse gastric cancer	137215
CDK4*	No	Yes	123829	9p21.3	Monoallelic	Melanoma susceptibility	609048
CDKN1B	No	Yes	600778	12p13.1	Monoallelic	Multiple endocrine neoplasia type IV	610755
CDKN1C	No	Yes	600856	11p15.4	Monoallelic	Beckwith-Wiedemann Syndrome	130650
CDKN2A	Yes	Yes	600160	9p21.3	Monoallelic	Melanoma susceptibility	606719 / 155755 / 155601
CDKN2B	No	Yes	600431	9p21.3	Monoallelic	Renal cancer susceptibility	14700
CEBPA	No	Yes	116897	19q13.11	Monoallelic	Acute myeloid leukaemia susceptibility	601626
CEP57	No	Yes	607951	11q21	Biallelic	Mosaic variegated aneuploidy syndrome 2	614114
CHEK2	No	Yes	604373	22q12.1	Monoallelic	Breast cancer susceptibility	114480
CYLD	No	Yes	605018	16q12.1	Monoallelic	Familial cylindromatosis	132700 / 601606 / 605041
DDB2	No	Yes	60811	11p11.2	Biallelic	Xeroderma pigmentosum (E)	278740
DICER1 [#]	No	Yes	606241	14q32.13	Monoallelic	Familial pleuropulmonary blastoma tumour predisposition syndrome	601200 / 138800 / 180295
DIS3L2	No	Yes	614184	2q37.1	Biallelic	Perlman syndrome	267000
EGFR*	No	Yes	131550	7p11.2	Monoallelic	Non small cell lung cancer susceptibility	211980

EPCAM	No	Yes	185535	2p21	Monoallelic	Lynch syndrome	613244
ERCC2	No	Yes	126340	19q13.32	Biallelic	Xeroderma pigmentosum (D)	278730
ERCC3	No	Yes	133510	2q14.3	Biallelic	Xeroderma pigmentosum (B)	610651
ERCC4	No	Yes	133520	16p13.12	Biallelic	Xeroderma pigmentosum (F)	278760
ERCC4	No	Yes	133520	16p13.12	Biallelic	Fanconi Anaemia (Q)	615272
ERCC5	No	Yes	133530	13q33.1	Biallelic	Xeroderma pigmentosum (G)	278780
ESR2	No	Yes	601163	14q23.2-q23.3	Monoallelic	Familial Medullary Thyroid Carcinoma	155240
EXT1	No	Yes	608177	8q24.11	Monoallelic	Multiple Exostoses, type 1	133700
EXT2	No	Yes	608210	11p11.2	Monoallelic	Multiple Exostoses, type 2	133701
EZH2	No	Yes	6011573	7q36.1	Biallelic	Weaver syndrome	277590
FANCA	No	Yes	607139	16q24.3	Biallelic	Fanconi anaemia (A)	227650
FANCB	No	Yes	300515	Xp22.2	Biallelic	Fanconi anaemia (B)	300514
FANCC	No	Yes	613899	9q22.32	Biallelic	Fanconi anaemia (C)	227645
FANCD2	No	Yes	613984	3p25.3	Biallelic	Fanconi anaemia (D2)	227646
FANCE	No	Yes	613976	6p21.31	Biallelic	Fanconi anaemia (E)	600901
FANCF	No	Yes	613897	11p14.3	Biallelic	Fanconi anaemia (F)	603467
FANCG	No	Yes	602956	9p13.3	Biallelic	Fanconi anaemia (G)	614082
FANCI	No	Yes	611360	15q26.1	Biallelic	Fanconi anaemia (I)	609053

FANCL	No	Yes	608111	2p16.1	Biallelic	Fanconi anaemia (L)	614083
FANCM	No	Yes	609644	14q21.2	Biallelic	Fanconi anaemia?	PS227650
FH	No	Yes	136850	1q43	Monoallelic	Hereditary leiomyomatosis and renal cell cancer	150800
					Biallelic	Fumarase deficiency (no known tumour predisposition)	606812
FLCN	No	Yes	607273	17p11.2	Monoallelic	Birt-Hogg-Dube syndrome	135150
GATA2	No	Yes	137295	3q21.3	Monoallelic	Acute myeloid leukemia susceptibility	614038 / 614172 / 601626 / 614286
GPC3	No	Yes	300037	Xq26.2	Monoallelic (XLR)	Simpson-Golabi-Behmel Syndrome	312870
HIF2A	No	Yes	603349	2p21	Monoallelic	Paraganglioma susceptibility	PS168000
HNF1A	No	Yes	142410	12q24.31	Monoallelic	Renal cancer susceptibility	144700
HOXB13	No	Yes	604607	17q21.31	Monoallelic	Prostate cancer susceptibility	176807
HRAS*	No	Yes	190020	11p15.5	Monoallelic	Costello Syndrome	218040
KIT*	Yes	Yes	164920	4q12	Monoallelic	Familial gastrointestinal stromal tumours	606764
MAX [§]	Yes	Yes	154950	14q23.3	Monoallelic	Familial Paraganglioma-Pheochromocytoma Syndrome	171300

MEN1	Yes	Yes	613733	11q13.1	Monoallelic	Multiple endocrine neoplasia type I	131100
MET*	Yes	Yes	164860	7q31.2	Monoallelic	Familial papillary renal cell cancer type 1	605074
MLH1	Yes	Yes	120436	3p22.2	Monoallelic	Lynch Syndrome	PS120435
MSH2	Yes	Yes	609309	2p21	Biallelic Monoallelic	Congenital mismatch repair deficiency Lynch Syndrome	276300 PS120435
MSH6	Yes	Yes	600678	2p16.3	Biallelic Monoallelic	Congenital mismatch repair deficiency Lynch Syndrome	276300 PS120435
MUTYH	Yes	Yes	604933	1p34.1	Biallelic	Congenital mismatch repair deficiency MUTYH associated polyposis	276300 608456
NBN	No	Yes	602667	8q21.3	Biallelic	Nijmegen Breakage Syndrome	251260
NF1 [#]	Yes	Yes	613113	17q11.2	Monoallelic	Neurofibromatosis type I	16220
NF2 [#]	Yes	Yes	607379	22q12.2	Monoallelic	Neurofibromatosis type II	101000
NSD1	No	Yes	606681	5q35.3	Monoallelic	Sotos Syndrome	117550
PALB2	No	Yes	610355	16p12.2	Mononallelic	Breast cancer susceptibility	114480
					Biallelic	Fanconi anaemia (N)	610832
PDGFRA*	Yes	Yes	173490	4q12	Monoallelic	Familial gastrointestinal stromal tumor	606764
PHOX2B	No	Yes	603851	4p13	Monoallelic	Neuroblastoma susceptibility	613013
PMS1	No	Yes	600258	2q32.2	Monoallelic	Lynch Syndrome	PS120435
PMS2	Yes	Yes	#614337	7p22.1	Monoallelic	Lynch Syndrome	PS120435

POLD1	No	Yes	174761	19q13.33	Biallelic Monoallelic	Congenital mismatch repair deficiency Colorectal cancer susceptibility	276300 612591
POLE	No	Yes	174762	12q24.33	Monoallelic	Colorectal cancer susceptibility	615083
PRF1	No	Yes	170280	10q22.1	Biallelic	Familial Hemophagocytic lymphohistiocytosis,(associated with tumour predisposition?)	267700
PRKAR1A	Yes	Yes	188830	17q24.2	Mono-allelic	Carney complex	160980
PTCH1 [#]	Yes	Yes	601309	9q22.32	Mono-allelic	Gorlin syndrome	109400
PTEN	Yes	Yes	601728	10q23.31	Mono-allelic	Cowden Syndrome	158350
RAD51C	No	Yes	602774	17q22	Mono-allelic	Ovarian cancer susceptibility	16700
					Biallelic	Fanconi Anaemia (O)	613390
RAD51D	No	Yes	602954	17q12	Mono-allelic	Breast - ovarian cancer susceptibility	PS604370
RB1 [#]	Yes	Yes	614041	13q14.2	Monoallelic	Hereditary retinoblastoma	180200
RECQL4	No	Yes	603780	8q24.3	Biallelic	Rothmund-Thompson Syndrome	268400
RET*	Yes	Yes	164761	10q11.21	Monoallelic	Multiple endocrine neoplasia, Familial medullary thyroid cancer	171400 / 162300 / 155240
RHBDF2*	No	Yes	614404	17q25.1	Monoallelic	Tylosis with oesophageal cancer	148500
RUNX1	No	Yes	151385	21q22.12	Monoallelic	Acute myeloid leukaemia, Familial platelet disorder with associated myeloid malignancy	601626 / 601399
SBDS	No	Yes	607444	7q11.21	Biallelic	Schwachman-Diamond Syndrome	260400

SDHAF2	Yes	Yes	613019	11q12.2	Monoallelic	Familial Parangangioma- Pheochromocytoma Syndrome	PS168000
SDHA	Yes	Yes	600857	5p15.33	Monoallelic	Familial Parangangioma-Pheochromocytoma Syndrome	PS168000
SDHB	Yes	Yes	185470	1p36.13	Monoallelic	Familial Parangangioma-Pheochromocytoma Syndrome	PS168000
SDHC	Yes	Yes	602413	1q23.3	Monoallelic	Familial Parangangioma-Pheochromocytoma Syndrome	PS168000
SDHD [§]	Yes	Yes	602690	11q23.1	Monoallelic	Familial Parangangioma-Pheochromocytoma Syndrome	PS168000
SLX4	No	Yes	613278	16p13.3	Biallelic	Fanconi anaemia (P)	613951
SMAD4	Yes	Yes	600993	18q21.2	Monoallelic	Juvenile Polyposis Syndrome	174900
SMARCA4	No	Yes	603254	19p13.2	Monoallelic	Rhabdoid tumour predisposition syndrome- 2 Small cell Ca ovary hypercalcaemic type	PS609322 N/A
SMARCB1 [#]	Yes	Yes	601607	22q11.23	Monoallelic	Rhabdoid Predisposition Syndrome	PS609322
SMARCE1	Yes	Yes	#603111	17q21.2	Monoallelic	Meningioma susceptibility	607174
STK11	Yes	Yes	602216	19p13.3	Monoallelic	Peutz-Jeghers Syndrome	175200
SUFU [#]	No	Yes	607035	10q24.32	Monoallelic	Familial medulloblastoma Basal cell naevus syndrome	607174 / 109400
TMEM127	Yes	Yes	613403	2q11.2	Monoallelic	Familial Parangangioma-Pheochromocytoma Syndrome	PS168000

TP53	Yes	Yes	191170	17p13.1	Monoallelic	Li Fraumeni Syndrome	151623
TSC1	Yes	Yes	#191100	9q34.13	Monoallelic	Tuberous sclerosis	PS191100
TSC2	Yes	Yes	191092	16p13.3	Monoallelic	Tuberous sclerosis	PS191100
VHL [#]	Yes	Yes	608537	3p25.3	Monoallelic	Von Hippel Lindau Syndrome	193300
WRN	No	Yes	604611	8p12	Biallelic	Werner Syndrome	277700
WT1 [#]	Yes	Yes	607102	11p13	Monoallelic	WAGR Familial Wilms tumour Denys-Drash Frasier Syndrome	194072 / 194070 / 194080 / 136680
XPA	No	Yes	611153	9q22.33	Biallelic	Xeroderma pigmentosum (A)	278700
XPC	No	Yes	613208	3p25.1	Biallelic	Xeroderma pigmentosum (C)	27820

[§], paternal transmission of mutant allele associated with tumour risk; *, gain of function; #, heterozygous deletion mutant allele associated with substantial childhood onset cancer risk

Table S2. CNVs detected involving a CPG in the Stage 1 Pilot Cohort Analysis.

Patient	CPG	Del / gain of CPG	Co-ordinates of CNV affecting CPG	CNV: benign / pathological / unrelated to clinical features	CNV dn or inh	Other array / cytogenetic findings	Other array / cytogenetic findings: benign / pathological / unrelated	Additional notes	Age at array (m)	Sex F/M
P001	BMPR1A	gain	arr[GRCh37] 10q22.3q23.2(81,489,155-89,047,672)x3	unrelated	inh	Nil	N/A	No relevant FHx	31	F
P002	BMPR1A	gain	arr[NCBI36] 10q22.3q23.2(81,618,854-88,977,697)x3	pathogenic	unknown	Nil	N/A	Nil	60	M
P003	BMPR1A	del	arr[GRCh37] 10q22.3q23.2(81,489,155-88,847,906)x1	pathogenic	dn	Nil	N/A	Nil	13	M
P004	BMPR1A	del	arr[GRCh37] 10q22.3q23.2(81,489,155-89,189,038)x1	pathogenic	dn	Nil	N/A	Nil	1	M
P005	BMPR1A	del	arr[GRCh37] 10q22.3q23.2(81,628,948-89,189,038)x1	pathogenic	inh	Nil	N/A	No relevant FHx	0	M
P006	BMPR1A & PTEN	del	arr[GRCh37] 10q23.1q23.31(87,785,872-90,301,307)x1	pathogenic	dn	Nil	N/A	Nil	0	F
P007	MET*	gain	arr[GRCh37] 7q31.2(114,687,978-116,355,918)x3	unrelated	inh	Nil	N/A	No relevant FHx	0	F
P008	MSH2 & MSH6	gain	arr[NCBI36] 2p22.2p16.2(37,472,079-54,403,333)x3	pathogenic	dn	Nil	n/a	Child has inherited unbalanced form of balanced deletion / insertion event on chr2 from a carrier parent	312	F
P009	NF1	gain	arr[NCBI36] 17q11.2(25,997,842-27,385,919.5)x3	unrelated	inh	Nil	N/A	No relevant FHx	0	M

P010	PMS2	gain [#]	arr[GRCh37] 7p22.3p21.3(54,215- 7,690,132)x3	pathogenic	unknown	46,XY,der(22)t(7;22)(p21.3 ;p11)	pathogenic	Likely child inherited unbalanced form of parental translocation. Both parental samples not available.	50	M
P011	PRKAR1A	gain	arr[GRCh37] 17q24.2q24.3(61,652,704- 66,662,580)x3	pathogenic	unknown	Nil	N/A	Nil	55	F
P012	PTEN	gain	arr[GRCh37] 10q23.31(89,635,555- 89,665,005)x3	unrelated	inh	arr[GRCh37] 15q13.2q13.3(30,491,443- 32,509,897)x3	unrelated	No relevant FHx. Child has in inherited one duplication from each parent. Partial gain of PTEN.	1	F
P013	RB1	gain	13q14.11q21.1(RP11- 125A7->RP11-200F15)x3	uncertain significance	inh	Nil	N/A	No relevant FHx. Analysis by BAC array	180	M
P014	RB1	gain	arr[GRCh37] 13q14.11q21.2(43,517,174 -60,107,850)x3	pathogenic	inh	Nil	N/A	No relevant FHx	192	F
P015	SDHA	del	arr[GRCh37] 5p15.33(22,179- 4,163,877)x1	pathogenic	dn	Nil	N/A	Nil	8	F
P016	SDHA	del	arr[GRCh37] 5p15.33(86,236-401,759)x1	uncertain significance	inh	arr[GRCh37] 7q35(146,175,061- 146,376,898)x1 46,XY,t(4;18)(q23;q23)	uncertain significance	FHx unknown. Child has inherited two deletions inherited from one parent and a balanced translocation from the other parent.	2	M
P017	SDHD	gain	arr[GRCh37] 11q23.1(111,883,595- 112,272,219)x3	unrelated	inh	arr[GRCh37] 2p13.1p12(74,433,160- 75,699,530)x3	unrelated	No relevant FHx. Likely two separate duplications inherited from one parent (no FISH undertaken).	175	F

P018	SDHD	gain	arr[GRCh37] 11q22.3q23.1(110,281,343-112,218,364)x3	uncertain significance	unknown	Nil	N/A	FHx unknown	8	F
P019	SMARCB1	gain	arr[GRCh37] 22q11.23(23,720,201-24,959,798)x3	unrelated	unknown	Nil	N/A	FHx unknown	0	M
P020	SMARCB1	gain	arr[GRCh37] 22q11.23(23,822,957-24,178,146)x3	uncertain significance	unknown	Nil	N/A	No relevant FHx	124	F
P021	TMEM127	gain	arr[GRCh37] 2q11.1q11.2(96,545,380-98,013,837)x3	unrelated	inh	Nil	N/A	No relevant FHx	1	F
P022	TMEM127	del	arr[GRCh37] 2q11.2(95,910,348-97,570,502)x1	uncertain significance	unknown	Nil	N/A	Nil	35	M
P023	TMEM127	del	arr[GRCh37] 2q11.1q11.2(96,766,590-98,206,184)x1	unrelated	inh	Nil	N/A	No relevant FHx	6	M
P024	TP53	gain	arr[GRCh37] 17p13.1(7,394,419-7,772,158)x3	uncertain significance	inh	arr[GRCh37] 10p15.3(226,113-332,378)x3, arr[GRCh37] 10p15.3(536,734-816,599)x3	uncertain significance	FHx unknown. All 3 duplications inherited from one parent.	5	F
P025	TP53	gain	arr[GRCh37] 17p13.1(7,572,205-7,583,268)x3	unrelated	inh	Nil	N/A	No relevant FHx. Partial gain of TP53.	179	M
P026	TSC2	gain [#]	arr[NCBI36] 16p13.3p13.13(12,798-10,656,496)x3	pathogenic	inh	46,XY,ish der(10)t(10;16)(q26.2;p13.13)(10ptel-,16ptel+)	pathogenic	Child has inherited unbalanced rearrangement from balanced carrier parent.	0	F
P027	TSC2	gain [#]	arr[NCBI36] 16p13.3p12.3(12,798-17,285,210)x3	pathogenic	dn	46,XX,der(1)t(1;16)(q44;p12.3)dn	pathogenic	Nil	9	F
P028	TSC2	gain [#]	arr[GRCh37] 16p13.3(93,748-3,702,950)x3	pathogenic	dn	46,XY,der(3)t(3;7)(p26.1;p21)dn, der(7)t(7;16)(p21;p16.3)dn , arr[GRCh37] 3p26.3p26.1(93,979-8,325,145)x1 dn	pathogenic	Nil	50	M

P029	TSC2	del	arr[GRCh37] 16p13.3(2,097,019- 2,099,039)x1dn	pathogenic	dn	Nil	N/A	TS clinically diagnosed subsequently. Deletion exons 1-2 TSC2 on minimum co- ordinates. Deletion exons 1-2 and part of exon 3 on maximum co- ordinates, arr[GRCh37] 16p13.3(2,047,5 54-2,100,464)x1. Pathogenic deletions of exon 3 and 5' UTR to exon 3 been described in TS (32-33).	7	M
P030	VHL	gain [#]	arr[GRCh37] 3p26.1p24.2(7,543,632- 24,901,101)x3	pathogenic	dn	45,XY,psu dic(3;21)dup(3)(3qter- >3p26.2::3p26.2- >3p25.1::21p11.1)dn	pathogenic	Nil	104	M
P031	VHL	gain [#]	3p26.1 to 3p24.3 (RP11- 277D17->RP11-208G16)x3	pathogenic	dn	46,XX,der(3)t(3;6)(p26.1;q 25.2)dup(3)(p26.1p24.3)dn , arr cgh 3p26.3p26.1(RP11-86C13- >RP11-324K11)x1 dn, 6q25.2q27(RP1-66H9- >RP11-226I21)x3 dn	pathogenic	Nil	0	F

del, deletion; FHx, family history; dn, de novo; inh, inherited; * oncogene; [#] presence of a complex chromosomal rearrangement; F, female; M, male

Table S3. CNVs detected involving a CPG in the Stage 2 Extended Cohort Analysis.

Patient	CPG	Del / gain of CPG	Co-ordinates of CNV affecting CPG	CNV: benign / pathological / unrelated to clinical features	CNV dn or inh	Other array / cytogenetic findings	Other array / cytogenetic findings: benign / pathological / unrelated	additional notes	age at array (m)	Sex F/M
P101	APC	deletion	arr[GRCh37] 5q15-q23.1(95,864,493-115,563,383)x1	pathogenic	dn	t(5;8)(q15;q13) dn	N/A	nil	205	female
P102	BLM & FANCI	deletion	arr[GRCh37] 15q25.3q26.1(87,891,894-92,197,207)x1	pathogenic	unknown	nil	N/A	nil	12	male
P103	BMPR1A	deletion	arr[GRCh37] 10q23.2(88,197,182-88,680,492)x1	unrelated	inh	t(1;10)(p32;q23.2) inh	unrelated	No FHx relevant to cancer gene. Deletion exons 1-10 BMPR1A on minimum co-ordinates. Maximum co-ordinates, arr[GRCh37] 10q23.2(88,150,393-88,828,085)x1 encompasses BMPR1A entirely. Pathogenic deletions of exons 1-3 and 2-11 been described (34-35).	26	male
P104	BMPR1A	deletion	arr[GRCh36] 10q22.3q23.2(81,631,898-88,930,398)x1	pathogenic	dn	nil	N/A	nil	175	male
P105	BRIP1	deletion	arr[GRCh37] 17q23.1q23.2(58,172,677-60,395,815)x1	pathogenic	unknown	nil	N/A	nil	102	male
P106	CHEK2	deletion	arr[GRCh36] 22q12.1(26,802,174-27,739,571)x1	uncertain significance	inh	nil	N/A	No FHx relevant to cancer gene	177	male
P107	CHEK2	deletion	arr[GRCh37] 22q12.1q12.2(27,988,300-29,622,742)x1	uncertain significance	dn	arr[GRCh37] 5p15.2(12,260,190-13,141,797)x1, arr[GRCh37] 15q13.3(31,972,643-32,509,932)x3	both uncertain significance	one additional CNV inherited from each parent	195	female
P108	FH	deletion	arr[GRCh37] 1q43q44(240,871,091-247,124,412)x1	pathogenic	dn	nil	N/A	nil	2	male

P109	FH	deletion	arr[GRCh37] 1q43(239,940,368- 243,128,788)x1	pathogenic	dn	nil	N/A	nil	47	male
P110	FLCN	deletion	arr[GRCh37] 17p11.2(16,637,872- 20,294,010)x1	pathogenic	dn	nil	N/A	nil	1	male
P111	FLCN	deletion	arr[GRCh37] 17p11.2(16,637,872- 20,219,455)x1	pathogenic	dn	nil	N/A	nil	12	female
P112	FLCN	deletion	arr[GRCh37] 17p11.2(16,637,872- 20,294,010)x1	pathogenic	unknown	nil	N/A	nil	33	male
P113	FLCN	deletion	arr[GRCh37] 17p11.2(16,782,547- 20,294,010)x1	pathogenic	dn	nil	N/A	nil	40	female
P114	FLCN	deletion	arr[GRCh37] 17p11.2(16,637,872- 20,294,010)x1	pathogenic	dn	nil	N/A	nil	45	male
P115	FLCN	deletion	arr[GRCh37] 17p11.2(16,637,872- 20,294,010)x1	pathogenic	unknown	nil	N/A	nil	63	female
P116	FLCN	deletion	arr[GRCh37] 17p11.2(16,637,872- 20,219,455)x1	pathogenic	unknown	nil	N/A	nil	95	male
P118	FLCN	deletion	arr[GRCh37] 17p12p11.2(15,801,2 94-20,524,000)x1	pathogenic	dn	nil	N/A	nil	106	male
P119	FLCN	deletion	arr[GRCh37] 17p11.2(16,637,872- 20,219,455)x1	pathogenic	unknown	nil	N/A	nil	136	female
P120	FLCN	deletion	arr[GRCh37] 17p11.2(16,637,872- 20,294,010)x1	pathogenic	unknown	nil	N/A	nil	444	female
P121	HRAS*	gain#	arr[GRCh37] 11p15.5p15.2(113,08 2-14,430,533)x3.	pathogenic	inh	46,XX,del(5)(p14.3p15.1)inh, der(5)t(5;11)(p15.31;p15.2)in h. arr[GRCh37] 5p15.33p15.31(22,149- 9,700,223)x1,5p15.1p14.3(16 ,168,384-22,925,861)x1	pathogenic	Child has inherited from each parent (i) unbalanced form of familial t(5;11)(p15.31;p15.2) (ii) familial del(5)(p14.3p15.1) associated with learning difficulties. Same	0	female

									individual as below.		
P121	SDHA	deletion#	arr[GRCh37] 5p15.33p15.31(22,14 9-9,700,223)x1	pathogenic	inh	46,XX,del(5)(p14.3p15.1)inh, der(5)t(5;11)(p15.31;p15.2)in h. arr[GRCh37] 5p15.1p14.3(16,168,384- 22,925,861)x1,11p15.5p15.2(113,082,14,430,533)x3	pathogenic	Child has inherited from each parent (i) unbalanced form of familial t(5;11)(p15.31;p15.2) (ii) familial del(5)(p14.3p15.1) associated with learning difficulties. Same individual as above.	0	female	
P122	HRAS*	gain#	arr[GRCh37] 11p15.5(113,082- 2,550,805)x3	pathogenic	inh	arr[GRCh37] 2q37.3(237,463,855- 243,087,748)x1	pathogenic	Child has inherited unbalanced form of parental ish t(2;11)(q37.3;p15.5)	6	female	
P123	KIT* and PDGFRA*	deletion	arr[GRCh37] 4q12q13.1(53,850,05 8-65,512,919)x1	pathogenic	dn	nil	N/A	nil	292	female	
P124	MAX	deletion	arr[GRCh37] 14q23.3(65,538,709- 67,351,711)x1	uncertain significance	dn	nil	N/A	Not known if deletion on pat or mat chr.	100	male	
P125	MET*	deletion	arr[GRCh37] 7q22.3q31.2(106,871 ,009-122,986,270)x1	pathogenic	dn	nil	N/A	nil	162	female	
P126	MET*	deletion	arr[GRCh37] 7q31.1q31.31(109,95 8,035- 117,946,370)x1	pathogenic	dn	nil	N/A	nil	272	female	
P127	MET*	gain#	arr[GRCh37] 7q21.3q36.3(94,257, 592-159,124,141)x3	pathogenic	dn	46,X,der(X)t(X;7)(p21.3;q21.3) . arr[GRCh37] Xp22.33p21.3(310,953- 28,515,804)x1	pathogenic	nil	29	female	
P128	NSD1	deletion	arr[GRCh37] 5q35.2q35.3(174,897 ,894-177,013,956)x1	pathogenic	dn	nil	N/A	nil	0	male	
P129	PDGFRα *	gain	min: arr[GRCh37] 4q12(54,873,967- 55,081,970)x3 max: arr[GRCh37] 4q12(54,830,498- 55,133,838)x3	uncertain significance	unknown	nil	N/A	Maximum region of CNV contains all of exons 1-6 and part of exon 7 of transcript NM_006206.4 of PDGFRα	33	male	
P130	PMS1	deletion	arr[GRCh36] 2q32.2q33.1(189,294 ,117-200,158,719)x1	pathogenic	dn	nil	N/A	nil	57	male	

P131	PMS2	deletion	arr[GRCh37] 7p22.1(5,151,574- 6,745,570)x1	pathogenic	dn	nil	N/A	nil	6	male
P132	PMS2	deletion	arr[GRCh36] 7p22.1(5,337,139- 6,263,352)x1	pathogenic	dn	nil	N/A	nil	30	male
P133	PMS2	deletion	arr[GRCh37] 7p22.1(5,617,810- 6,350,273)x1	uncertain significance	unknown	nil	N/A	nil	80	male
P134	POLD1	deletion	arr[GRCh37] 19q13.33(50,126,448 -51,026,193)x1	pathogenic	unknown	nil	N/A	nil	46	male
P135	POLE	deletion	arr[GRCh37] 12q24.33(133,237,07 7-133,773,393)x1	uncertain significance	unknown	arr[GRCh37] 2p21(44,518,437-44,542,918)x3	uncertain significance	Deletion exons 1-25 POLE on minimum co- ordinates. Maximum co- ordinates, arr[GRCh37] 12q24.33(133,153,306- 133,851,895)x1, encompasses POLE.	122	male
P136	RB1	deletion	arr[GRCh37] 13q13.1q31.1(33,786 ,863-83,585,442)x1	pathogenic	dn	nil	N/A	subsequently developed RB	0	female
P137	RB1	deletion	arr[GRCh37] 13q14.11q21.32(41,7 17,885- 66,044,521)x1	pathogenic	dn	nil	N/A	subsequently developed RB as did MZ twin	3	male
P138	RUNX1	deletion	arr[GRCh36] 21q22.11q22.12(33,8 33,276- 35,618,531)x1	pathogenic	dn	arr[GRCh36] 5q33.2(155,149,896- 155,496,459)x3	inh. uncertain significance	child previously noted to have unexplained low platelet count	137	male
P139	SDHA	deletion	arr[GRCh37] 5p15.33p14.1(22,149 -24,835,505)x1	pathogenic	unknown	nil	N/A	nil	0	male
P140	SDHA	deletion	arr[GRCh37] 5p15.33p15.1(22,149 -18,133,322)x1	pathogenic	unknown	arr[GRCh37] 5p15.1p14.1(18,215,614- 26,972,861)x3	uncertain significance	nil	3	female
P141	SDHA	deletion	arr[GRCh37] 5p15.33p14.3(22,149 -21,217,291)x1	pathogenic	dn	nil	N/A	nil	6	female
P142	SDHA	deletion	arr[GRCh36] 5p15.33(75,149- 3,292,621)x1	uncertain significance	inh	nil	N/A	nil	16	male

P143	SDHA	deletion	arr[GRCh37] 5p15.33p15.1(22,149-15,151,743)x1	pathogenic	dn	nil	N/A	nil	26	male
P144	SDHA	deletion	arr[GRCh37] 5p15.33p15.2(22,149-11,213,706)x1	pathogenic	unknown	nil	N/A	nil	460	male
P145	SDHB	deletion	arr[GRCh36] 1p36.21- p36.12(15,422,198-21,235,203)x1	pathogenic	dn	nil	N/A	nil	74	male
P146	SDHD	deletion	arr[GRCh37] 11q22.3q23.3(105,289,128-116,644,381)x1	pathogenic	dn	nil	N/A	del on pat chr	13	female
P147	SMARCA4	deletion	min: arr[GRCh37] 19p13.2(10,466,712-11,053,974)x1 max: arr[GRCh37] 19p13.2(10,418,713-11,117,391)x1	uncertain significance	unknown	nil	N/A	Maximum region of CNV deletes exons 1-14 of SMARCA4. Minimum region not involve SMARCA4.	50	male
P148	SMARCB1	deletion	arr[GRCh36] arr 22q11.21q11.23(20,052,254-22,923,820)x1	pathogenic	unknown	nil	N/A	nil	148	male
P149	TMEM127	deletion	arr[GRCh36] 2q11.1q11.2(94,892,764-100,915,841)x1	pathogenic	dn	nil	N/A	nil	97	male
P150	TMEM127	deletion	arr[GRCh37] 2q11.1q11.2(96,766,564-97,039,740)x1	uncertain significance	unknown	nil	N/A	nil	191	male

del, deletion; FHx, family history; dn, de novo; inh, inherited; * oncogene; # presence of a complex chromosomal rearrangement; F, female; M, male

Table S4. CNVs detected involving a CPG in both the Stage 1 and Stage 2 Cohort Analyses.

Patient	CPG	Del / gain of CPG	Co-ordinates of CNV affecting CPG	CNV: benign / pathological / unrelated to clinical features	CNV dn or inh	Other array / cytogenetic findings	Other array / cytogenetic findings: benign / pathological / unrelated	Additional notes	Age at array (m)	Sex
P101	APC	del	arr[GRCh37] 5q15-q23.1(95,864,493-115,563,383)x1	Pathogenic	dn	t(5;8)(q15;q13) dn	N/A	Nil	205	F
P103	BMPR1A	del	arr[GRCh37] 10q23.2(88,197,182-88,680,492)x1	Unrelated	inh	t(1;10)(p32;q23.2) inh	unrelated	No FHx relevant to cancer gene. Deletion exons 1-10 BMPR1A on minimum co-ordinates. Maximum co-ordinates, arr[GRCh37] 10q23.2(88,150,393-88,828,085)x1 encompass BMPR1A. Pathogenic deletions of exons 1-3 and 2-11 have been described (34-35)	26	M
P104	BMPR1A	del	arr[GRCh36] 10q22.3q23.2(81,631,898-88,930,398)x1	Pathogenic	dn	nil	N/A	Nil	175	M
P003	BMPR1A	del	arr[GRCh37] 10q22.3q23.2(81,489,155-88,847,906)x1	Pathogenic	dn	Nil	N/A	Nil	13	M
P004	BMPR1A	del	arr[GRCh37] 10q22.3q23.2(81,489,155-89,189,038)x1	Pathogenic	dn	Nil	N/A	Nil	1	M
P005	BMPR1A	del	arr[GRCh37] 10q22.3q23.2(81,628,948-89,189,038)x1	Pathogenic	inh	Nil	N/A	No relevant FHx	0	M
P006	BMPR1A & PTEN	del	arr[GRCh37] 10q23.1q23.31(87,785,872-90,301,307)x1	Pathogenic	dn	Nil	N/A	Nil	0	F
P123	KIT* and PDGFRA*	del	arr[GRCh37] 4q12q13.1(53,850,058	Pathogenic	dn	nil	N/A	nil	292	F

			-65,512,919)x1								
P124	MAX	del	arr[GRCh37] 14q23.3(65,538,709- 67,351,711)x1	uncertain significance	dn	nil	N/A	Not known if del on pat or mat chr.	100	M	
P125	MET*	del	arr[GRCh37] 7q22.3q31.2(106,871, 009-122,986,270)x1	Pathogenic	dn	nil	N/A	nil	162	F	
P126	MET*	del	arr[GRCh37] 7q31.1q31.31(109,958 ,035-117,946,370)x1	Pathogenic	dn	nil	N/A	nil	272	F	
P127	MET*	gain#	arr[GRCh37] 7q21.3q36.3(94,257,5 92-159,124,141)x3	Pathogenic	dn	46,X,der(X)t(X;7)(p21.3;q 21.3). arr[GRCh37] Xp22.33p21.3(310,953- 28,515,804)x1	pathogenic	nil	29	F	
P007	MET*	gain	arr[GRCh37] 7q31.2(114,687,978- 116,355,918)x3	Unrelated	inh	Nil	N/A	No relevant FHx	0	F	
P129	PDGFR α *	gain	min: arr[GRCh37] 4q12(54,873,967- 55,081,970)x3 max: arr[GRCh37] 4q12(54,830,498- 55,133,838)x3	uncertain significance	unknown	nil	N/A	Maximum region of CNV contains all of exons 1-6 and part of exon 7 of transcript NM_006206.4 of PDGFR α	33	M	
P131	PMS2	del	arr[GRCh37] 7p22.1(5,151,574- 6,745,570)x1	pathogenic	dn	nil	N/A	nil	6	M	
P132	PMS2	del	arr[GRCh36] 7p22.1(5,337,139- 6,263,352)x1	pathogenic	dn	nil	N/A	nil	30	M	
P133	PMS2	del	arr[GRCh37] 7p22.1(5,617,810- 6,350,273)x1	uncertain significance	unknown	nil	N/A	nil	80	M	
P136	RB1	del	arr[GRCh37] 13q13.1q31.1(33,786, 863-83,585,442)x1	pathogenic	dn	nil	N/A	subsequently developed RB	0	F	
P137	RB1	del	arr[GRCh37] 13q14.11q21.32(41,71 7,885-66,044,521)x1	pathogenic	dn	nil	N/A	subsequently developed RB as did MZ twin	3	M	
P139	SDHA	del	arr[GRCh37] 5p15.33p14.1(22,149-	pathogenic	unknown	nil	N/A	nil	0	M	

			24,835,505)x1								
P140	SDHA	del	arr[GRCh37] 5p15.33p15.1(22,149- 18,133,322)x1	pathogenic	unknown	arr[GRCh37] 5p15.1p14.1(18,215,614- 26,972,861)x3	uncertain significance	nil	3	F	
P141	SDHA	del	arr[GRCh37] 5p15.33p14.3(22,149- 21,217,291)x1	pathogenic	dn	nil	N/A	nil	6	F	
P142	SDHA	del	arr[GRCh36] 5p15.33(75,149- 3,292,621)x1	uncertain significance	inh	nil	N/A	nil	16	M	
P143	SDHA	del	arr[GRCh37] 5p15.33p15.1(22,149- 15,151,743)x1	pathogenic	dn	nil	N/A	nil	26	M	
P144	SDHA	del	arr[GRCh37] 5p15.33p15.2(22,149- 11,213,706)x1	pathogenic	unknown	nil	N/A	nil	460	M	
P121	SDHA	del#	arr[GRCh37] 5p15.33p15.31(22,149 -9,700,223)x1	pathogenic	inh	46,XX,del(5)(p14.3p15.1)ih, der(5)t(5;11)(p15.31;p15. 2)inh. arr[GRCh37] 5p15.1p14.3(16,168,384- 22,925,861)x1,11p15.5p1 5.2(113,082,14,430,533)x 3	pathogenic	Child has inherited from each parent (i) unbalanced form of familial t(5;11)(p15.31;p15. 2) (ii) familial del(5)(p14.3p15.1) associated with learning difficulties.	0	F	
P015	SDHA	del	arr[GRCh37] 5p15.33(22,179- 4,163,877)x1	pathogenic	dn	Nil	N/A	Nil	8	F	
P016	SDHA	del	arr[GRCh37] 5p15.33(86,236- 401,759)x1	uncertain significance	inh	arr[GRCh37] 7q35(146,175,061- 146,376,898)x1 46,XY,t(4;18)(q23;q23)	uncertain significance	FHx unknown. Child has inherited two dels inherited from one parent and a balanced translocation from the other parent.	2	M	
P145	SDHB	del	arr[GRCh36] 1p36.21- p36.12(15,422,198- 21,235,203)x1	pathogenic	dn	nil	N/A	nil	74	M	
P146	SDHD	del	arr[GRCh37] 11q22.3q23.3(105,289 ,128-116,644,381)x1	pathogenic	dn	nil	N/A	del on pat chr	13	F	
P148	SMARCB1	del	arr[GRCh36] arr	pathogenic	unknown	nil	N/A	nil	148	M	

			22q11.21q11.23(20,052,254-22,923,820)x1								
P149	TMEM127	del	arr[GRCh36] 2q11.1q11.2(94,892,764-100,915,841)x1	pathogenic	dn	nil	N/A	nil	97	M	
P150	TMEM127	del	arr[GRCh37] 2q11.1q11.2(96,766,564-97,039,740)x1	uncertain significance	unknown	nil	N/A	nil	191	M	
P022	TMEM127	del	arr[GRCh37] 2q11.2(95,910,348-97,570,502)x1	uncertain significance	unknown	Nil	N/A	Nil	35	M	
P023	TMEM127	del	arr[GRCh37] 2q11.1q11.2(96,766,590-98,206,184)x1	unrelated	inh	Nil	N/A	No relevant FHx	6	M	
P029	TSC2	del	arr[GRCh37] 16p13.3(2,097,019-2,099,039)x1dn	pathogenic	dn	Nil	N/A	TS clinically diagnosed subsequently. Deletion exons 1-2 TSC2 on minimum co-ordinates. Deletion exons 1-2 and part of exon 3 on maximum co-ordinates, arr[GRCh37] 16p13.3(2,047,554-2,100,464)x1. Pathogenic deletions of exon 3 and 5' UTR to exon 3 been described in TS (32-33).	7	M	

del, deletion; FHx, family history; dn, de novo; inh, inherited; * oncogene; # presence of a complex chromosomal rearrangement; F, female; M, male