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Subgroup-specific structural variation across 1,000 medulloblastoma genomes.

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Subgroup-specific structural variation across 1,000 medulloblastoma genomes

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Medulloblastoma, the most common malignant paediatric brain tumour, is currently treated with nonspecific cytotoxic therapies including surgery, whole-brain radiation, and aggressive chemotherapy. As medulloblastoma exhibits marked intertumoural heterogeneity, with at least four distinct molecular variants, previous attempts to identify targets for therapy have been underpowered because of small samples sizes. Here we report somatic copy number aberrations (SCNAs) in 1,087 unique medulloblastomas. SCNAs are common in medulloblastoma, and are predominantly subgroup-enriched. The most common region of focal copy number gain is a tandem duplication of *SNCAIP*, a gene associated with Parkinson's disease, which is exquisitely restricted to Group 4α. Recurrent translocations of *PVT1*, including *PVT1–MYC* and *PVT1–NDRG1*, that arise through chromothripsis are restricted to Group 3. Numerous targetable SCNAs, including recurrent events targeting TGF-β signalling in Group 3, and NF-κB signalling in Group 4, suggest future avenues for rational, targeted therapy.

Brain tumours are the most common cause of childhood oncological death, and medulloblastoma is the most common malignant paediatric brain tumour. Current medulloblastoma therapy including surgical resection, whole-brain and spinal cord radiation, and aggressive chemotherapy supplemented by bone marrow transplant yields five-year survival rates of 60–70%[1]. Survivors are often left with significant neurological, intellectual and physical disabilities secondary to the effects of these nonspecific cytotoxic therapies on the developing brain[2].

Recent evidence suggests that medulloblastoma actually comprises multiple molecularly distinct entities whose clinical and genetic differences may require separate therapeutic strategies[3–6]. Four principal subgroups of medulloblastoma have been identified: WNT, SHH, Group 3 and Group 4 (ref. 7), and there is preliminary evidence for clinically significant subdivisions of the subgroups[3,7,8]. Rational, targeted therapies based on genetics are not currently in use for medulloblastoma, although inhibitors of the Sonic Hedgehog pathway protein Smoothened have shown early promise[9]. Actionable targets for WNT, Group 3 and Group 4 tumours have not been identified[4,10]. Sanger sequencing of 22 medulloblastoma exomes revealed on average only 8 single nucleotide variants (SNVs) per tumour[11]. Some SNVs were subgroup-restricted (*PTCH1*, *CTNNB1*), whereas others occurred across subgroups (*TP53*, *MLL2*). We proposed that the observed intertumoural heterogeneity might have underpowered prior attempts to discover targets for rational therapy.

The Medulloblastoma Advanced Genomics International Consortium (MAGIC) consisting of scientists and physicians from 46 cities across the globe gathered more than 1,200 medulloblastomas which were studied by SNP arrays ($n = 1{,}239$; Fig. 1a, Supplementary Fig. 1 and Supplementary Tables 1–3). Medulloblastoma subgroup affiliation of 827 cases was determined using a custom nanoString-based RNA assay (Supplementary Fig. 2)[12]. Disparate patterns of broad cytogenetic gain and loss were observed across the subgroups (Fig. 1b and Supplementary Figs 3, 7, 8, 10 and 11). Analysis of the entire cohort using GISTIC2 (ref. 13) to discover significant 'driver' events delineated 62 regions of recurrent SCNA (Fig. 1c, Supplementary Fig. 4 and Supplementary Tables 4 and 5); analysis by subgroup increased sensitivity such that 110 candidate 'driver' SCNAs were identified, most of which are subgroup-enriched (Fig. 1c–e and Supplementary Table 6).

Twenty-eight regions of recurrent high-level amplification (copy number ≥ 5) were identified (Fig. 1d and Supplementary Table 7). The most prevalent amplifications affected members of the MYC family with *MYCN* predominantly amplified in SHH and Group 4, *MYC* in Group 3, and *MYCL1* in SHH medulloblastomas. Multiple genes/regions were exclusively amplified in SHH, including *GLI2*, *MYCL1*, *PPM1D*, *YAP1* and *MDM4* (Fig. 1d). Recurrent homozygous deletions were exceedingly rare, with only 15 detected across 1,087 tumours (Fig. 1e). Homozygous deletions targeting known tumour suppressors *PTEN*, *PTCH1* and *CDKN2A/B* were the most common, all enriched in SHH cases (Fig. 1e and Supplementary Table 7). Novel homozygous deletions included *KDM6A*, a histone-lysine demethylase deleted in Group 4. A custom nanoString CodeSet was used to verify 24 significant regions of gain across 192 MAGIC cases, resulting in a verification rate of 90.9% (Supplementary Fig. 5). We conclude that SCNAs in medulloblastoma are common, and are predominantly subgroup-enriched.

Subgroup-specific SCNAs in medulloblastoma

WNT medulloblastoma genomes are impoverished of recurrent focal regions of SCNA, exhibiting no significant regions of deletion and only a small subset of focal gains found at comparable frequencies in non-WNT tumours (Supplementary Figs 4, 6 and Supplementary Table 8). *CTNNB1* mutational screening confirmed canonical exon 3 mutations in 63 out of 71 (88.7%) WNT tumours, whereas monosomy 6 was detected in 58 out of 76 (76.3%) (Supplementary Fig. 6; Supplementary Table 9). Four WNT tumours (4/71; 5.6%) had neither *CTNNB1* mutation nor monosomy 6, but maintained typical WNT expression signatures. Given the size of our cohort and the resolution of the platform, we conclude that there are no frequent, targetable SCNAs for WNT medulloblastoma.

SHH tumours exhibit multiple significant focal SCNAs (Fig. 2a, Supplementary Figs 12, 15, 16 and Supplementary Tables 10 and 11). SHH enriched/restricted SCNAs included amplification of *GLI2* and deletion of *PTCH1* (Fig. 2a, e, f)[10]. *MYCN* and *CCND2* were among the most frequently amplified genes in SHH (Supplementary Table 6), but were also altered in non-SHH cases. Genes upregulated in SHH tumours (that is, SHH signature genes) are significantly over-represented among the genes focally amplified in SHH tumours

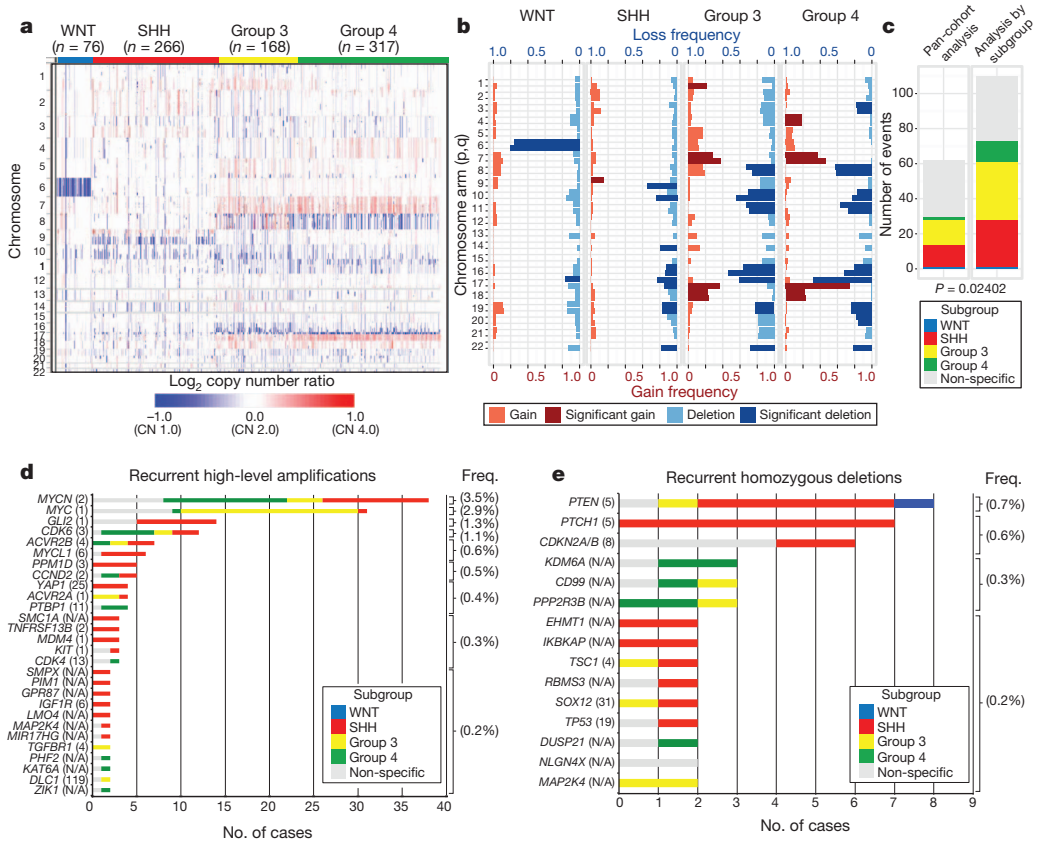

Figure 1 | Genomic heterogeneity of medulloblastoma subgroups. **a**, The medulloblastoma genome classified by subgroup. **b**, Frequency and significance (Q value ≤ 0.1) of broad cytogenetic events across medulloblastoma subgroups. **c**, Significant regions of focal SCNA identified by GISTIC2 in either pan-cohort or subgroup-specific analyses. **d**, **e**, Recurrent high-level amplifications (**d**, segmented copy number (CN) ≥ 5) and homozygous deletions (**e**, segmented CN ≤ 0.7) in medulloblastoma. The number of genes mapping to the GISTIC2 peak region (where applicable) is listed in brackets after the suspected driver gene, as is the frequency of each event.

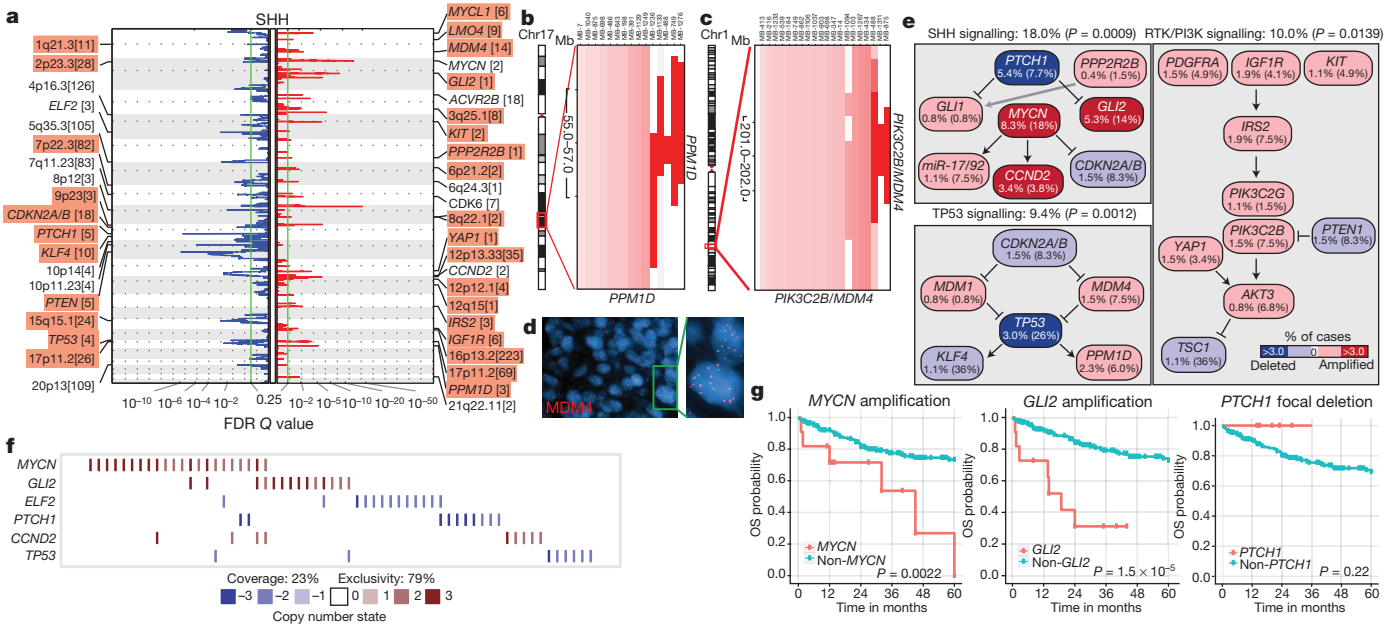

Figure 2 | Genomic alterations affect core signalling pathways in SHH medulloblastoma. **a**, GISTIC2 significance plot of amplifications (red) and deletions (blue) observed in SHH. The number of genes mapping to each significant region are included in brackets and regions enriched in SHH are shaded red. **b**, **c**, Recurrent amplifications of *PPM1D* (**b**) and *PIK3C2B*/*MDM4* (**c**) are restricted to SHH. **d**, Fluorescence *in situ* hybridization (FISH) validation of *MDM4* amplification. **e**, SHH signalling, TP53 signalling and RTK/PI3K signalling represent the core pathways genomically targeted in SHH. *P* values indicate the prevalence with which the respective pathway is targeted in SHH versus non-SHH cases (Fisher's exact test). Frequencies of focal and broad (parentheses) SCNAs are listed. **f**, Mutual exclusivity analysis of focal SCNAs in SHH. **g**, Clinical implications of SCNAs affecting *MYCN*, *GLI2* or *PTCH1* in SHH (log-rank tests).

($P = 0.001–0.02$, permutation tests; Supplementary Fig. 9). Recurrent amplification of SHH signature genes has clinical implications, as amplification of downstream transcriptional targets could mediate resistance to upstream SHH pathway inhibitors[14].

Novel, SHH-enriched SCNAs included components of TP53 signalling, including amplifications of *MDM4* and *PPM1D*, and focal deletions of *TP53* (Fig. 2a–e). Targetable events, including amplifications of IGF signalling genes *IGF1R* and *IRS2*, PI3K genes *PIK3C2G* and *PIK3C2B*, and deletion of *PTEN* were restricted to SHH tumours (Fig. 2a, c, e). Importantly, focal events affecting genes in the SHH pathway were largely mutually exclusive and prognostically significant (Fig. 2f, g). Many of the recurrent, targetable SCNAs identified in SHH medulloblastoma (*IGF1R*, *KIT*, *MDM4*, *PDGFRA*, *PIK3C2G*, *PIK2C2B* and *PTEN*) have already been targeted with small molecules for treatment of other malignancies, which might allow rapid translation for targeted therapy of subsets of SHH patients (Supplementary Table 16). Novel SHH targets identified here are excellent candidates for combinatorial therapy with Smoothened inhibitors, to avoid the resistance encountered in both humans and mice[9,14,15].

Group 3 and Group 4 medulloblastomas have generic names as comparatively little is known about their genetic basis, and no targets for rational therapy have been identified[7]. *MYC* amplicons are largely restricted to Group 3, whereas *MYCN* amplicons are seen in Group 4 and SHH tumours (Fig. 1d)[3,4]. Indeed, *MYC* and *MYCN* loci comprise the most significant regions of amplification observed in Group 3 and Group 4, respectively (Fig. 3a, b, Supplementary Figs 13, 14, 17–20 and Supplementary Tables 12–15). Group 3 *MYC* amplicons were mutually exclusive from those affecting the known medulloblastoma oncogene *OTX2* (ref. 16) and were highly prognostic (Supplementary Fig. 21)[3,16]. Type II activin receptors, *ACVR2A* and *ACVR2B* and family member *TGFBR1* are highly amplified in Group 3 tumours, indicating deregulation of TGF-β signalling as a driver event in Group 3 (Fig. 3c–e and Supplementary Fig. 22). The Group 3-enriched medulloblastoma oncogene *OTX2* is a prominent target of TGF-β signalling in the developing nervous system[17] and TGF-β pathway inhibitors *CD109* (ref. 18), *FKBP1A* (refs 19 and 20) and *SNX6* (ref. 20) are recurrently deleted in Group 3 (Fig. 3a, d). SCNAs in TGF-β pathway genes were heavily enriched in Group 3 ($P = 5.37 \times 10^{-5}$, Fisher's exact test) and found in at least 20.2% of cases, indicating that TGF-β signalling represents the first rational target for this poor prognosis subgroup (Fig. 3d). Similarly, novel deletions affecting regulators of the NF-κB pathway, including *NFKBIA* (ref. 21) and *USP4* (ref. 22) were identified in Group 4 (Supplementary Fig. 23), proposing that NF-κB signalling may represent a rational Group 4 therapeutic target.

Network analysis of Group 3 and Group 4 SCNAs illustrates the different pathways over-represented in each subgroup. Only TGF-β signalling is unique to Group 3 (Fig. 3e). In contrast, cell-cycle control, chromatin modification and neuronal development are all Group 4-enriched. Cumulatively, the dismal prognosis of Group 3 patients, the lack of published targets for rational therapy, and the prior targeting of TGF-β signalling in other diseases suggest that TGF-β may represent an appealing target for Group 3 rational therapies (Supplementary Table 16).

SNCAIP tandem duplication is common in Group 4

Although Group 4 is the most prevalent medulloblastoma subgroup, its pathogenesis remains poorly understood. The most frequent SCNA observed in Group 4 (33/317; 10.4%) is a recurrent region of single copy gain on chr5q23.2 targeting a single gene, *SNCAIP* (synuclein, alpha interacting protein) (Fig. 4a and Supplementary Fig. 24). *SNCAIP*, encodes synphilin-1, which binds to α-synuclein to promote the formation of Lewy bodies in the brains of patients with Parkinson's disease[23,24]. Additionally, rare germline mutations of *SNCAIP* have been described in Parkinson's families[25]. Large insert, mate-pair, whole-genome sequencing (WGS) demonstrates that

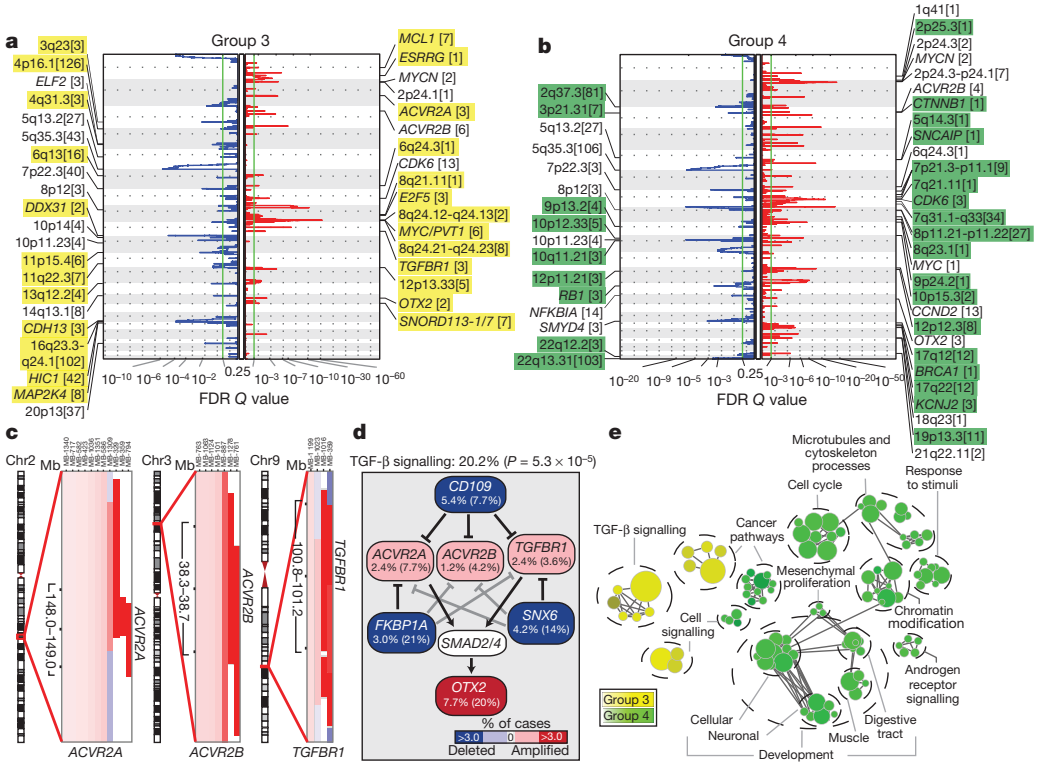

Figure 3 | The genomic landscape of Group 3 and Group 4 medulloblastoma. **a**, **b**, GISTIC2 plots depicting significant SCNAs in Group 3 (**a**) and Group 4 (**b**) with subgroup-enriched regions shaded in yellow and green, respectively. **c**, Recurrent amplifications targeting type II (*ACVR2A* and *ACVR2B*) and type I (*TGFBR1*) activin receptors in Group 3. **d**, Recurrent SCNAs affecting the TGF-β pathway in Group 3 ($P = 5.73 \times 10^{-5}$, Fisher's exact test). Frequencies of focal and broad (parentheses) SCNAs are listed. **e**, Enrichment map of gene sets affected by SCNAs in Group 3 versus Group 4.

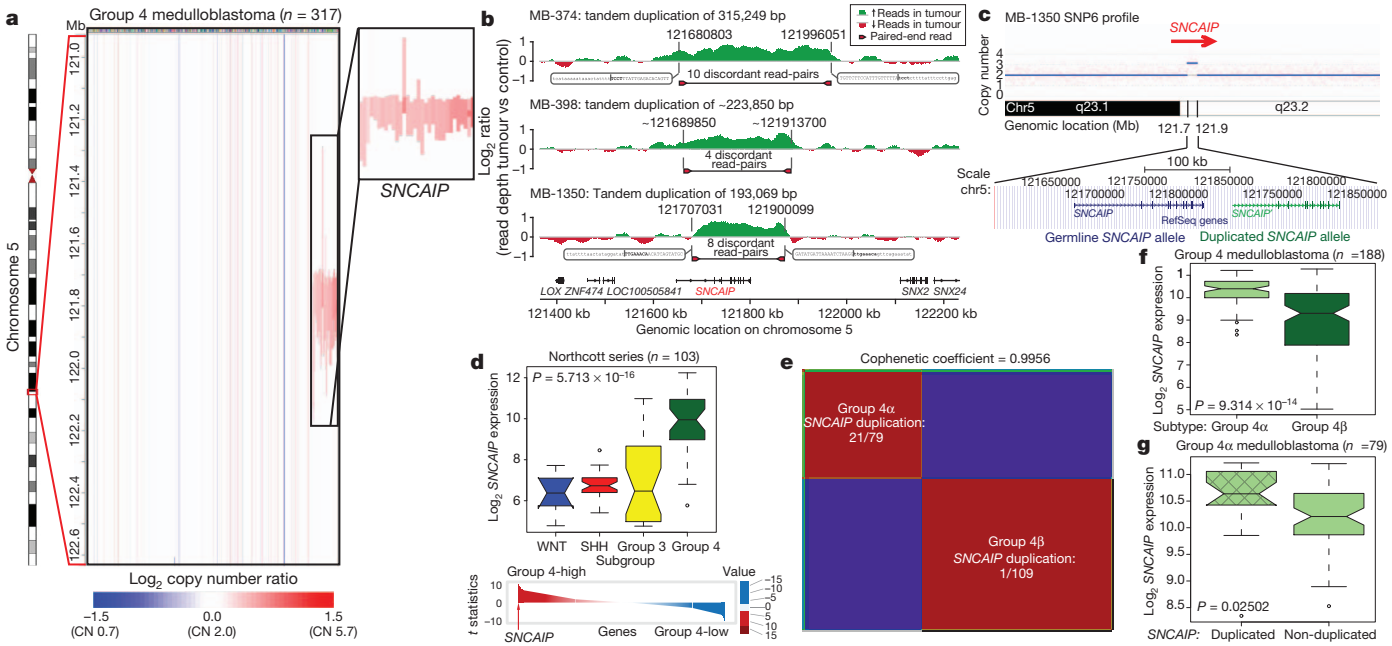

Figure 4 | Tandem duplication of *SNCAIP* defines a novel subtype of Group 4. **a**, Highly recurrent, focal, single-copy gain of *SNCAIP* in Group 4. **b**, Paired-end mapping verifies recurrent tandem duplication of *SNCAIP* in Group 4. **c**, Schematic representation of *SNCAIP* tandem duplication. **d**, *SNCAIP* is a Group 4 signature gene. Upper panel, *SNCAIP* expression across subgroups in a published series of 103 primary medulloblastomas. Error bars depict the minimum and maximum values, excluding outliers. Lower panel, *SNCAIP* ranks among the top 1% (rank, 39th out of 16,758) of highly expressed genes in Group 4. **e**, NMF consensus clustering of 188 expression-profiled Group 4 tumours supports two transcriptionally distinct subtypes designated 4α and 4β (cophenetic coefficient = 0.9956). 21 out of 22 *SNCAIP* duplicated cases belong to Group 4α ($P = 3.12 \times 10^{-8}$, Fisher's exact test). **f**, *SNCAIP* expression is significantly elevated in Group 4α versus 4β ($P = 9.31 \times 10^{-14}$, Mann–Whitney test). **g**, Group 4α cases harbouring *SNCAIP* duplication exhibit a ~1.5-fold increase in *SNCAIP* expression. **f**, **g**, Error bars depict the minimum and maximum values, excluding outliers.

SNCAIP copy number gains arise from tandem duplication of a truncated *SNCAIP* (lacking non-coding exon 1), inserted telomeric to the germline *SNCAIP* allele (Fig. 4b, c and Supplementary Fig. 25). Affymetrix SNP6 array profiling of patient-matched germline material confirmed that *SNCAIP* duplications are somatic (Supplementary Fig. 26), and subsequent whole-transcriptome sequencing (RNA-Seq) of select Group 4 cases ($n = 5$) verified that *SNCAIP* is the only gene expressed in the duplicated region (Supplementary Fig. 27). Analysis of published copy number profiles for 3,131 primary tumours[26] and 947 cancer cell lines[27] (total of 4,078 cases) revealed only four cases with apparent duplication of *SNCAIP*, all of which were inferred as Group 4 medulloblastomas (data not shown). We conclude that *SNCAIP* duplication is a somatic event highly specific to Group 4 medulloblastoma.

Re-analysis of 499 published medulloblastoma expression profiles confirmed that *SNCAIP* is one of the most highly upregulated Group 4 signature genes (Fig. 4d and Supplementary Fig. 28). Profiling of 188 Group 4 tumours on expression microarrays followed by consensus non-negative matrix factorization (NMF) clustering delineates two subtypes of Group 4 (4α and 4β; Fig. 4e and Supplementary Fig. 29). Strikingly, 21 out of 22 *SNCAIP* duplicated cases belonged to Group 4α ($P = 3.12 \times 10^{-8}$, Fisher's exact test). *SNCAIP* is more highly expressed in Group 4α than 4β (Fig. 4f), and 4α samples with tandem duplication showed approximately 1.5-fold increased expression, consistent with gene dosage (Fig. 4g and Supplementary Figs 35 and 36). Group 4α exhibits a relatively balanced genome compared to 4β (Supplementary Figs 30–32), and several 4α cases harbour *SNCAIP* duplication in conjunction with i17q and no other SCNAs (Supplementary Fig. 33). Importantly, *SNCAIP* duplications are mutually exclusive from other prominent SCNAs in Group 4, including *MYCN* and *CDK6* amplifications (Supplementary Fig. 34).

PVT1 fusions arise via chromothripsis in Group 3

Although recurrent gene fusions have recently been discovered in solid tumours, none have been reported in medulloblastoma. RNA-Seq of Group 3 tumours ($n = 13$) identified two independent gene fusions in two different tumours (MB-182 and MB-586), both involving the 5′ end of *PVT1*, a non-coding gene frequently co-amplified with *MYC* in Group 3 (Fig. 5a, b, Supplementary Fig. 37 and Supplementary Tables 17 and 18). Sanger sequencing confirmed a fusion transcript consisting of exons 1 and 3 of *PVT1* fused to the coding sequence of *MYC* (exons 2 and 3) in MB-182, and a fusion involving *PVT1* exon 1 fused to the 3′ end of *NDRG1* in MB-586 (Fig. 5a, b).

Group 3 copy number data at the *MYC*/*PVT1* locus indicated that additional samples might harbour *PVT1* gene fusions (Fig. 5c). PCR with reverse transcription (RT–PCR) profiling of select Group 3 cases confirmed *PVT1-MYC* fusions in at least 60% (12/20) of *MYC*-amplified cases (Fig. 5d and Supplementary Table 19). Fusion transcripts included many other portions of chr8q, with up to four different genomic loci mapping to a single transcript, a pattern reminiscent of chromothripsis[28,29] (Fig. 5d). WGS performed on four *MYC*-amplified Group 3 tumours harbouring *PVT1* fusion transcripts identified a series of complex genomic rearrangements on chr8q (Fig. 5e, f, Supplementary Fig. 38 and Supplementary Tables 20 and 21). Chromosome 8 copy number profile for MB-586 (*PVT1-NDRG1*) derived from WGS showed that *PVT1* and *NDRG1* are structurally linked, as predicted by RNA-Seq, and several adjacent regions of 8q24 were extensively rearranged (Fig. 5e, f and Supplementary Table 21). Monte Carlo simulation suggests that this fragmented 8q amplicon arose through chromothripsis, a process of erroneous DNA repair following a single catastrophic event in which a chromosome is shattered into many pieces (Supplementary Fig. 39). Further examination of our copy number data set revealed rare examples of chromothripsis across subgroups (Supplementary Fig. 40), with only chr8 in Group 3 demonstrating statistically significant, region-specific chromothripsis ($Q = 0.0004$, false discovery rate (FDR)-corrected Fisher's exact test). Among Group 3 tumours, the occurrence of chr8q chromothripsis is correlated with deletion of chr17p (location of *TP53;* data not shown), in keeping with the association of loss of

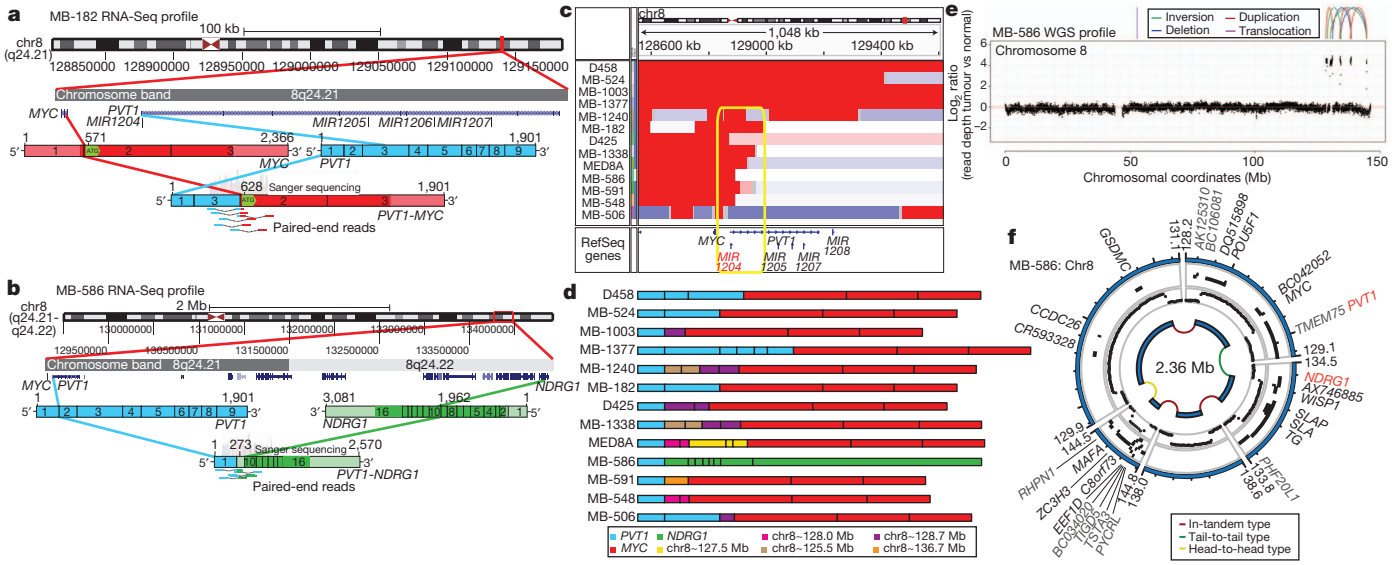

Figure 5 | Identification of frequent *PVT1-MYC* fusion genes in Group 3. **a**, **b**, RNA-Seq identifies multiple fusion transcripts driven by *PVT1* in Group 3. Schematics depict the structures of verified *PVT1-MYC* (**a**) and *PVT1-NDRG1* (**b**) fusion genes. **c**, Heat map of the *MYC/PVT1* locus showing a subset of 13 *MYC*-amplified Group 3 cases subsequently verified to exhibit *PVT1* gene fusions (shown in **d**). Yellow box highlights the common breakpoint affecting the first exon/intron of *PVT1*, including *miR-1204*. **d**, Summary of *PVT1* fusion transcripts identified in Group 3. **e**, **f**, WGS confirms complex patterns of rearrangement on chr8q24 in *PVT1* fusion (+) Group 3.

TP53 and chromothripsis recently described in medulloblastoma ($P = 0.0199$, Fisher's exact test)[28]. Whereas the *PVT1* locus has been suggested to be a genomically fragile site, we observe that the majority of *MYC*-amplified Group 3 tumours harbour *PVT1* fusions that arise through a process consistent with chromothripsis.

PVT1 is a non-coding host gene for four microRNAs, *miR-1204–miR-1207*. Previous studies have implicated *miR-1204* as a candidate oncogene that enhances oncogenesis in combination with *MYC*[30,31]. *PVT1* fusions identified in this study involve only *PVT1* exon 1 and *miR-1204*. Importantly, *miR-1204*, but not the adjacent *miR-1205* and *miR-1206*, is expressed at a higher level in *PVT1-MYC* fusion (+) Group 3 tumours compared to fusion (−) cases ($P = 0.0008$, Mann–Whitney test; Fig. 6a). To evaluate whether aberrant expression of *miR-1204* contributes to the malignant phenotype, we inhibited *miR-1204* in MED8A cells, a Group 3 medulloblastoma cell line with a confirmed *PVT1-MYC* fusion (Fig. 5d). Antagomir-mediated RNA interference of *miR-1204* had a pronounced effect on MED8A growth (Fig. 6b). A comparable reduction in proliferative capacity was achieved with knockdown of *MYC*. Conversely, the medulloblastoma cell line ONS76 exhibits neither *MYC* amplification nor a detectable *PVT1-MYC* fusion gene, and knockdown of *miR-1204* had no effect in this line (Fig. 6c).

PVT1 has been reported previously in fusion transcripts with a number of partners[30,32,33]. The most prevalent form of the *PVT1-MYC* fusion in Group 3 tumours lacks the first, non-coding exon of *MYC*, similar to forms of *MYC* that have been described in Burkitt's lymphoma[34] (Fig. 5a, d). The *PVT1* promoter contains two non-canonical E-boxes and can be activated by *MYC*[31]. This indicates a positive feedback model where *MYC* can reinforce its own expression from the *PVT1* promoter in *PVT1-MYC* fusion (+) tumours. Indeed, knockdown of *MYC* alone in MED8A cells resulted in diminished expression of both *MYC* and *miR-1204*, suggesting *MYC* may positively regulate *PVT1* (that is, *miR-1204*) expression in medulloblastoma cells (Supplementary Fig. 41).

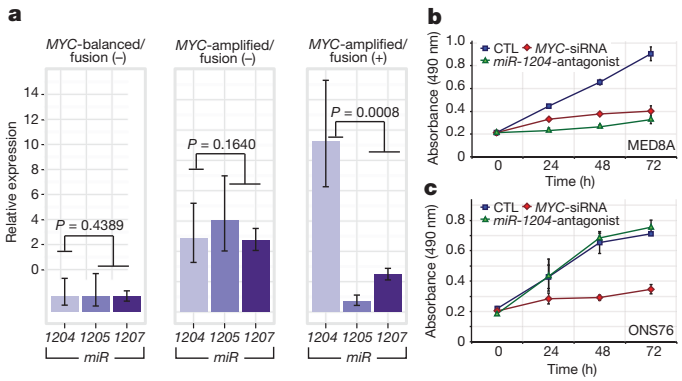

Figure 6 | Functional synergy between *miR-1204* and *MYC* secondary to *PVT1-MYC* fusion. **a**, Quantitative RT–PCR of *PVT1*-encoded microRNAs confirms upregulation of *miR-1204* in *PVT1-MYC* fusion (+) Group 3 tumours. *MYC*-balanced/fusion (−), $n = 4$; *MYC*-amplified/fusion (−), $n = 6$; *MYC*-amplified/fusion (+), $n = 8$. Error bars represent standard error of the mean (s.e.m.) and reflect variability among samples. **b**, **c**, Knockdown of *miR-1204* attenuates the proliferative capacity of *PVT1-MYC* fusion (+) MED8A medulloblastoma cells (**b**) but has no effect on fusion (−) ONS76 cells (**c**). Error bars represent the standard deviation (s.d.) of triplicate experiments. CTL, control.

Discussion

Medulloblastomas have few SNVs compared to many adult epithelial malignancies[11], whereas SCNAs seem to be quite common. Medulloblastoma is a heterogeneous disease[7], thereby requiring large cohorts to detect subgroup-specific events. Through the accumulation of >1,200 medulloblastomas in MAGIC, we have identified novel and significant SCNAs. Many of the significant SCNAs are subgroup-restricted, highly supporting their role as driver events in their respective subgroups.

Expression of synphilin-1 in neuronal cells results in decreased cell doubling time[35], decreased caspase-3 activation[36], decreased *TP53* transcriptional activity and messenger RNA levels, and decreased apoptosis[37]. Synphilin-1 is ubiquitinated by parkin, which is encoded by the hereditary Parkinson's disease gene *PARK2* (ref. 24), a candidate tumour suppressor gene[38]. Whereas patients with Parkinson's disease have an overall decreased risk of cancer, they may have an increased incidence of brain tumours[39,40]. As tandem duplications of *SNCAIP* are highly recurrent, stereotypical, subgroup-restricted, affect only a single gene, and as *SNCAIP*-duplicated tumours have few if any other SCNAs, *SNCAIP* is a probable driver gene, and merits investigation

as a target for therapy of Group 4α. Similarly, *PVT1* fusion genes are highly recurrent, restricted to Group 3, arise through a chromothripsis-like process, and are the first recurrent translocation reported in medulloblastoma.

We identify a number of highly targetable, recurrent, subgroup-specific SCNAs that could form the basis for future clinical trials (that is, PI3K signalling in SHH, TGF-β signalling in Group 3, and NF-κB signalling in Group 4). Activation of these pathways through alternative, currently unknown genetic and epigenetic events could increase the percentage of patients amenable to targeted therapy. We also identify a number of highly 'druggable' events that occur in a minority of cases. The cooperative, global approach of the MAGIC consortium has allowed us to overcome the barrier of intertumoural heterogeneity in an uncommon paediatric tumour, and to identify the relevant and targetable SCNAs for the affected children.

METHODS SUMMARY

All patient samples were obtained with consent as outlined by individual institutional review boards. Genomic DNA was prepared, processed and hybridized to Affymetrix SNP6 arrays according to manufacturer's instructions. Raw copy number estimates were obtained in dChip, followed by CBS segmentation in R. SCNAs were identified using GISTIC2 (ref. 13). Driver genes within SCNAs were inferred by integrating matched expressions, literature evidence and other data sets. Pathway enrichment of SCNAs was analysed with g:Profiler and visualized in Cytoscape using Enrichment Map. Fluorescence *in situ* hybridization (FISH) was performed as described previously[8,10]. Medulloblastoma subgroup was assigned using a custom nanoString CodeSet as described previously[12]. Tandem duplication of *SNCAIP* was confirmed by paired-end mapping as previously reported[28]. RNA was extracted, processed and hybridized to Affymetrix Gene 1.1 ST Arrays as recommended by the manufacturer. Consensus NMF clustering was performed in GenePattern. Gene fusions were identified from RNA-Seq data using Trans-ABySS. Medulloblastoma cell lines were maintained as described[10]. Proliferation assays were performed with the Promega CellTiter 96 Assay. Additional methods are detailed in full in Supplementary Methods.

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